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Diagnosis and Treatment of

Tumors of the Chest

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Contents

Introduction

During the past several decades great strides have been made in the fundamental knowledge of medical sciences In no other field has greater progress been made than in diseases of the chest. It has become inevitable that studies relating to these conditions should become more or less specialized, depending on organs affected and types of disease. Thus, such diseases may be presented anatomically, e.g., those of the tracheobronchial tree, pulmonary parenchyma, pleura, diaphragm, esophagus, mediastinum, cardiovascular system, etc., or etiologically, e g , inflammations, bacterial, viral, mycotic, parasitic, collagen diseases, diseases of industrial and congenital origin, and tumors, etc The need for a detailed description and presentation of etiologic factors and recent proven methods of treatment in particular fields of thoracic diseases requires space impossible to include in one cover to cover volume. It seems wise that the authors should choose to report investigations and treatment of particular disease groups separately. Dr Spain, who has had a wide clinical, laboratory and pathologic experience has wisely chosen to bring you, through his own observation and those of his distinguished coauthors, the soundest present day thoughts and observations on tumors of and within the thorax Pathogenesis, structural details, complications, diagnostic armamentaria and therapeutic measures

assures the reader a comprehensive and informative guide to the better understanding of the various tumors and their more efficient treatment.

Since its organization twenty-five years ago, The American College of Chest Physicians has encouraged and sponsored the education of the physician in the field of diseases of the chest. The College is proud to sponsor and recommend this fine volume, *Diagnosis and Treatment of Tumors of the Chest*, because of the excellent content therein and because it recognizes the present day need for detailed reporting of the various groups of abnormal entities This volume should prove useful not only as a text for specialists in thoracic disease, but also as an excellent reference work for undergraduate students and practitioners having a particular interest in fields closely related to diseases of the chest. It should also be valuable to workers interested in the clinical and research aspects of tumors in general

Donald R. McKay

Preface

ANY TEXT ATTEMPTING TO DEAL with the subject of neoplasms, even on the most practical clinical level, must do so within the frame of reference of the present state of our knowledge in the field of experimental and basic cancer research. At present there are many conflicting theories as to the etiology of the various forms of cancer. These include the well known virus concept, immunologic mechanisms, somatic mutations, and chemical and endocrine carcinogenesis. Despite the establishment of viruses as etiologic agents in many animal tumors, in only one human neoplasm (the skin wart) has a virus etiology been established at present. Currently, our basic knowledge of cancer consists of the following established facts (All else remains controversial, speculative and unproven.) Neoplasia consists of cells which proliferate with no restraint, in contrast to the normal growth of cells which is limited. Growth of the tumor may be related to changes in the host or to changes within the tumor cell itself. The former tumors are called dependent and the latter autonomous. Within the host, tumor growth may be altered by sustained excessive stimulation or a deficiency of natural restraining forces. Within the tumor itself, the rate of growth may be cytogenic or outside of the self-replicating apparatus of the cell. Some autonomous tumors respond to physical regulating mechanisms. Others do not. The general trend in malignant neoplasia is for progression, i.e., from bad to worse, from a good response to a poor response and from normal function to nonfunction. The differences between benign and malignant are poorly understood and it is unclear whether these should be grouped together as similar disease processes. Clearly, from the foregoing information there is nothing that can be of immediate practical help to the clinician in the definitive therapy of the patient with carcinoma. Despite recent advances in the synthesis of anticancer chemicals and further insight into antimetabolites and enzymatic behavior of cancer cells, chemotherapy at present only offers temporary relief in a limited number of instances. The clinician today must rely on the tried and tested procedures of early and accurate diagnosis and judicious surgical and radiation therapy. Early diagnosis today is helped by the improvement in our radiographic technics and the addition of various biopsy methods and exfoliative cytology. Treatment has benefited by better understanding of electrolytes, improved anesthesia and refined surgical procedures. Radiation therapy can be delivered in higher doses to more concentrated areas. It is hoped, but as yet unproven, that mass radiography and mass cytologic studies may provide the means for earlier diagnosis and a higher cure rate.

As yet, none of the results from any particular method of treatment have

been subjected to rigid biostatistical evaluation. For this reason, in addition to some overlapping of material in various chapters, one must also expect reasonable differences of opinion as to the best treatment for any particular type of tumor

An eminent leader in the field of cancer research has recently stated that it may well be that some simple practical methods, not necessarily related to the basic aspects of cancer growth, may bring a solution to the practical aspects of cancer control When this comes about, research into the basic mechanisms that produce cancer will rightly be regarded, partially at least, as an intellectual exercise. In this sense, the important discovery, to which this book devotes considerable space that cigarette smoking is a major cause of bronchogenic carcinoma, provides a means for eliminating the major portion of this form of cancer It is hoped that the material in this text will provide sufficient moral and scientific ammunition for the practicing chest clinician to devote sufficient time to the prevention of this form of cancer If and when this comes about, further studies on the biologic nature of bronchogenic cancer which are as yet not understood, will truly be in part an intellectual exercise

The title of this book is *Diagnosis and Treatment of Tumors of the Chest.* It is hoped that a revised edition or an entirely new book on the subject will eventually be entitled *Prevention, Diagnosis and Treatment of Tumors of the Chest*

The presentation of the material in this book is dedicated to the concept that research, education and patient care are the continuing, interrelated keystones on which the modern practice of medicine is based

DAVID M SPAIN, M.D.

Acknowledgments

SPECIAL THANKS ARE DUE to the Editorial Board and the individual contributors who so generously gave of their thoughts, effort and time. May Zachs and Gertrude Levine gave unstintingly of their time in preparation of the manuscript. *Finally, it should be recorded that this book was entirely* conceived, initiated and made possible under the guidance and auspices of the Executive Office of the American College of Chest Physicians.

CHAPTER 1

On The Etiology of Bronchogenic Carcinoma

By MICHAEL B. SHIMKIN, M.D

PRIMARY PULMONARY CARCINOMA HAS BEEN RECOGNIZED for well over a hundred years Descriptions of cases are to be found with increasing frequency in the medical writings of the nineteenth century In 1879, Harting and Hesse established that lung cancer accounted for a high proportion of pulmonary deaths that were the scourge of the Schneeberg miners, the first example of environmentally induced lung cancer.

Primary carcinoma of the lung, as all other major forms of neoplastic disease, has been described to occur in all human populations and many animal species that have been adequately studied. It has become increasingly more convincing from recent investigations that carcinoma of the lung represents a group of separable diseases The epidermoid and anaplastic morphologic types of bronchogenic carcinoma in man are associated with known environmental factors, occur more frequently in males than in females, and have shown an increase in incidence throughout the western world (Dunn, Doll) In contrast, adenocarcinoma of the lung appears to be much less related to known environmental factors, is more evenly distributed among males and females and has been relatively stable in incidence (Kreyberg) The bronchiolar carcinoma appears to be still another neoplastic entity, morphologically resembling the primary adenomatous tumor of the mouse and the infectious adenomatosis of sheep.

Primary pulmonary tumors in animals are usually of the adenomatous type, and the distribution by sex is approximately equal The lung tumor of the mouse has been studied extensively, and similar tumors are found spontaneously and can be induced with carcinogens in the rat and guinea pig Bronchogenic carcinoma resembling the human tumor has been induced in rats following exposure to radioactive inhalants (Cember and Watson)

Among domestic animals, pulmonary neoplasms have been described most frequently in dogs and in horses, probably because these species are permitted to live to older ages Individual case reports of lung cancer include wild animals in zoologic parks, such as a jaguar, a kangaroo and a civet There is also one report of an adenocarcinoma of the lung in a fowl (Shimkin, Steiner)

These general comparative descriptions lead to the following generalizations. (1) Lung cancer was known before industrialization was well advanced and before cigarettes existed; (2) the basic causes of lung cancer

are widely distributed among human and animal populations; (3) there are several neoplastic disease entities with diverse etiologies grouped under the anatomic designation of lung cancer, and (4) environmental inhalants can lead to the induction of lung cancer in man and in laboratory animals.

The Increase in Bronchogenic Carcinoma

About 30 years ago it began to be suspected that primary pulmonary cancer was being encountered more frequently The early impressions were based usually on autopsy series in which lung cancer became increasingly more prominent relative to other causes of death or other types of neoplasms It is primarily in retrospect that this rise in incidence was noted in the national vital statistics of the United States, Great Britain and other western European countries (Dunn). In the United States, even retrospective analysis of such statistics encounters the difficulties of interpreting changes in classification, incomplete coverage, and the inadequate evidence on which many of the early reports on neoplastic diseases are based (Milmore) For these reasons, the increase in lung cancer was a matter of serious debate, and it is only during the past decade that it has become clear that pulmonary cancer is a phenomenon that can be described as a neoplastic pandemic (figs. 1 and 2). And the incidence rates for successively younger cohorts continue to rise (fig. 3).

From a rare disease of 50 years ago, lung cancer has climbed to the first position of site-specific neoplastic deaths among men. In the vital statistics of the United States for 1956 it accounted for 29,000 deaths of which 25,000 were among males. In men over 50 years of age, more deaths are attributed to lung cancer than to all other respiratory diseases The recorded mortality is even higher in some western European countries and in Great Britain (Doll) Correction of crude mortality rates to relate them to a standard population of a fixed age distribution does not affect the trend of the rates

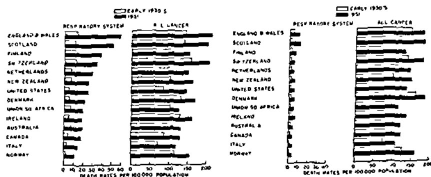


Fig 1—*Crude mortality rate for cancer in selected countries; (left)* men; *(right)* women (from Dunn)

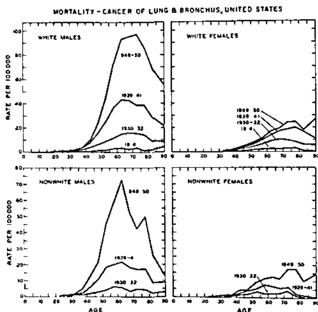


Fig 2—Death rates for cancer of the lung in the United States, selected years 1914–1950, classified by age, sex and race (from Dorn and Cutler)

appreciably, indicating that the aging of the population is not a prominent feature in this increase (Dunn).

Primary pulmonary cancer is not an easy disease to diagnose, and in many early autopsy series the correct clinical diagnosis was missed in more than 90 per cent of the cases. The past 50 years have seen the introduction of the roentgenogram and the fluoroscope, the bronchoscope and thoracotomy, tuberculosis and other respiratory diseases have decreased as causes of death, and antibiotics have unmasked neoplasms that were previously obscured by pneumonia, hospital records and vital statistics have improved What, then, is the basis for believing that lung cancer has truly increased, rather than that the figures merely reflect better recognition and reporting, and other statistical artifacts?

This particular question, and its various ramifications, has been the subject of many astute analyses, conferences and international symposia. The following are among the many facts that support the thesis of a real increase in lung cancer and, conversely, that are inconsistent with the explanation of spurious statistics for the major proportion of the increase:

1 The increase in death rates from lung cancer continues, and is just as evident now as 20 years ago During this time there has been no other neoplastic site or type that has manifested a comparable increase

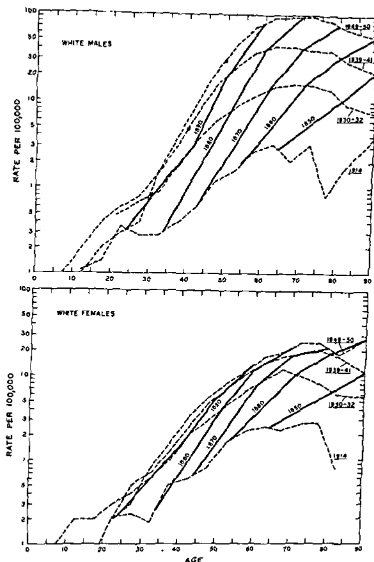


Fig 3—Death rates for cancer of the lung for white males (*top*) and white females (*bottom*), by age, United States, selected 1914–1950, arranged to show cohort rates (from Dorn and Cutler)

2 The increase is more marked for males than for females, and this disproportion has become greater during the more recent years *It is unlikely that greater diagnostic acumen,* or better recording, is exercised for men than for women

3 The increase has been approximately the same among physicians in the United States and in Great Britain as among the general population of the two countries Presumably physicians have better access to and use of diagnostic technics than the general population

4 The increase has been most marked for epidermoid and anaplastic carcinoma of the lung, while adenocarcinoma has remained relatively stable

The Role of Environmental Factors

Speculations regarding the possible reasons for the increase in lung cancer began to appear in the medical literature as soon as the increase was suspected. The increase was widespread, it was affecting males to a much greater extent than females, and it seemed more prominent in urban centers than in rural areas These characteristics made it reasonable to consider that the increase was not due to any genetic or constitutional changes in the populations, and that specific local industrial situations could not account for the phenomenon

One possibility entertained was that pulmonary cancer was the end result of some infectious process such as tuberculosis or influenza Tuberculosis was considered of primary importance by Ewing, but this thesis is no longer compatible with the decreasing incidence of tuberculosis while lung cancer continues to rise Morphologic studies on lungs of individuals dying during the influenza pandemic of 1918 to 1919 revealed epithelial proliferation of the bronchioles which in many cases invaded the surrounding tissue and resembled a neoplastic process (Jordan) It was suggested that an increase in lung cancer among survivors might be anticipated as a consequence However, morbidity and mortality from influenza affected men and women equally, which is not in accord with the sex incidence of lung cancer The prediction has been finally laid to rest by direct studies of veterans of World War I, which failed to elicit an association between influenzal pneumonia and the subsequent development of bronchogenic carcinoma (Case and Lea)

Other favored candidates included the environmental agents to which the general population, but particularly the males, were being exposed to an increasingly greater concentration It is, of course, more than likely that on the wall of some Egyptian tomb are inscriptions attesting that disease is the result of the corruptions of civilization and the stresses of life Nevertheless, it is undeniable that the past 50 years have seen the appearance of new hazards and the accelerated exposure to old dangers In the field of neoplasms, the British surgeon Percival Pott in 1775 showed that chronic contact with soot led to the appearance of scrotal carcinoma in chimneysweeps and the patient Japanese pathologists, Yamagiwa and Ichikawa in *1915 produced carcinoma on the ears of rabbits painted with tar.* These findings suggested that similar materials in the inhaled air deserved exploration in the search for causative environmental agents that may be involved in the rising toll from pulmonary cancer

Such candidate materials are not difficult to find Since 1926, in the United States there have occurred two to sixfold increases in motor vehicle registration, fuel oil sales, motor fuel consumption and asphalt highways (fig 4). There also has been a 35 per cent increase in the per capita use of

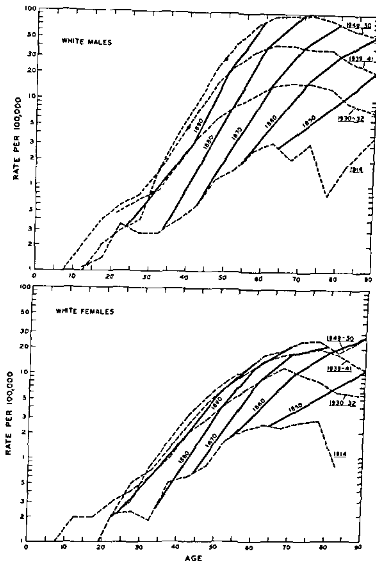


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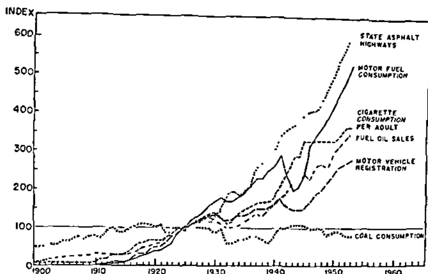


Fig 4—*Trends in selected environmental factors in the United States, 1900–1953, using* 1926 as the reference point (100) (from Hammond)

tobacco, but a fivefold increase in the use of cigarettes with a resultant drop in other forms of tobacco products (Milmore and Conover). And, of course, *there has been increasing industrialization,* and concentration of populations in and around urban centers with heavy contamination of the atmosphere with a wide variety of industrial and individually produced pollutants

In 1956 Campbell began a series of investigations in England which demonstrated that dust from tarred roads and exhaust fumes of automobiles could increase the frequency of pulmonary tumors and induce some skin carcinomas in mice In 1938 the newly formed National Cancer Institute selected pulmonary cancer as one of its topics of research emphasis and a number of the earliest research fellows were selected for this work. Tars extracted from atmospheric dusts collected in several cities were demonstrated to be carcinogenic, in that on subcutaneous injection they produced sarcomas in mice (Leiter et al) These data were in general agreement with the observation that lung cancer occurred more frequently in cities than in rural areas, and helped to stimulate the campaigns for atmospheric pollution abatement in such cities as Pittsburgh and St. Louis. Since proponents for dirty air are few and far between, no one seriously questioned whether adenomatous pulmonary tumors and subcutaneous sarcomas in mice had much to do with bronchogenic carcinoma in man.

Industrial Factors

Another active field of research dealing with possible environmental factors in lung cancer is represented by the scanty statistics that have been

gathered laboriously on workers in various industries Such data are often obtained in the face of considerable opposition from management, since bothersome compensation problems can be posed by the findings It is not surprising, therefore, that in many instances possible hazards remain as plausible shrewd guesses rather than established epidemiologic findings (Hueper)

There are at least five occupations in which lung cancer is an unquestionable hazard Among the miners of Schneeberg and Joachimsthal, who dug silver for the Fuggers of the sixteenth century and now extract radioactive ores for the Kremlin, lung cancer may well be the first cause of mortality. Whether radioactivity per se, a combination of metallic ore dusts or the action of both are responsible is still far from clear (Lorenz) Recently, the thesis of radioactivity has gained favor by the production of bronchogenic carcinomas in rats breathing or insufflated with radioactive cesium or sulfur Further research work on the relationship of radiation exposure and the occurrence of lung cancer in man should have high priority, since mankind is entering an era of radiation, and it would be useful to know what that means in terms of increased leukemia, mutations and, perhaps, lung cancer as well

Chromate workers also have an increased risk to lung cancer, estimated to be between 14 to 80 times that of the general population (Doll) Until recently, no tumors had been produced in experimental animals with chromates, although it must be admitted that the published works did not indicate that the investigators were trying very hard Hueper now has reported the appearance of neoplasms in rats injected subcutaneously with chromate ore roast

Asbestosis has been shown acceptably to lead to the development of lung cancer in man The workers in this industry with exposures sufficient to cause pulmonary lesions develop ten times the incidence of lung cancer to be expected in the general population (Doll)

There are a number of other occupations in which the increase in the risk to lung cancer is of more modest proportions on the order of double that of the general male population These groups include workers in coal gas factories and iron ore miners (Doll).

Breslow et al. conducted a retrospective study on the relationship of occupation to lung cancer, and found that 7 occupational groups, particularly those exposed to metallic particles, fumes and products of metallic combustion, had a high representation among lung cancer cases However, when these data were adjusted for cigarette smoking, only steam fitters, boilermakers and asbestos workers had an increase in lung cancer that approached statistical significance

The findings on groups of industrial occupation establish that a number of environmental inhalants can increase the risk of developing lung cancer.

If chromate and asbestos are adequate examples, materials that are carcinogenic for the lung are different from the classical carcinogens for the skin of man, at least quantitatively The reaction process appears to involve inhalation and protracted, direct contact of the agent with the bronchial mucosa, usually accompanied by pathologic changes in the lung substance.

For every worker who remains in one occupation for many years, there are many individuals whose employment is more temporary. In addition, around most industries there is some contamination of the air with the products of the industrial process, so that families of workers and other residents of the locality are exposed to the materials, although at lower concentrations These peripheral exposures of the general population probably account for some of the increased incidence of lung cancer in man, but the proportion that can be ascribed to these factors cannot be a predominant one. There are at least two reasons for this conclusion: A general atmospheric contaminant should affect males and females more equally than experience indicates, but more important is that another environmental factor, the smoking of tobacco, was shown by direct studies to be of greater relative importance

The Role of Tobacco Smoking

The relationship of smoking to lung cancer has been postulated for many years, but scientific demonstration of the relationship became more firmly established in 1950. In that year, 5 adequate investigations were published, all showing an association between lung cancer and smoking, especially of cigarettes These studies were of retrospective design; that is, patients with lung cancer were questioned regarding their habits and other events in their past history, and the answers compared with those of "control" patients without lung cancer, matched for age, sex and other characteristics. In these, and in at least 15 additional studies of this type now published from 8 countries, it has been uniformly reported that more patients with lung cancer smoked, and a greater proportion were "heavy" smokers of cigarettes than the control group.

Individual retrospective epidemiologic studies can be criticized on several statistical grounds, but since these studies were conducted with various modifications of selection and technics, the specific criticisms which have been advanced do not apply to all of them (Cornfield et al.). For example, the possible bias introduced by presumed overstatement of recalled smoking habits by patients with lung cancer is excluded in several studies in which histories were obtained before the diagnosis was established Patients in whom the presumptive diagnosis of lung cancer was not proved resembled controls rather than lung cancer patients in regard to their smoking histories.

The statistical findings of the reported increase of lung cancer in many countries and of the retrospective studies showing an association between smoking and lung cancer were among the main topics considered by an international conference on the epidemiology of lung cancer held in Louvain in 1952 (Steiner) Among the conclusions of the conference was that a significant part of the lung cancer increase was real, and that there was an association between cigarette smoking and bronchogenic carcinoma Further research was urged. Atmospheric pollution, occupational hazards and other environmental factors were additional areas in which expanded research was recommended.

The conclusions arrived at in 1952 were based primarily on statistical data At that time, pathogenetic and experimental data on the effects of tobacco smoke on the lung were scanty and conflicting The American Cancer Society provided effective leadership in expanding research in these and other areas, through a series of research conferences and a broad special program of grant support for research on lung cancer.

In 1951 to 1952, 2 investigations were begun using the prospective method to study the association of lung cancer to smoking In England, Doll and Hill sent questionnaires to 60,000 physicians regarding their smoking habits, and began to follow the 40,000 from whom they receive answers as well as the 20,000 who did not reply. The American Cancer Society initiated a study under the direction of Hammond and Horn, in which volunteer workers obtained smoking histories on 188,000 males 50 to 69 years of age The men were followed for 44 months Dorn of the National Cancer Institute began a third large study in 1954, using over 250,000 veterans of World War I as the observation group

The answers from these 3 massive investigations were in agreement among themselves and with the previous results from retrospective studies. The early results of the prospective studies that initially could have been attributed to bias in original selection of subjects not only did not disappear, but became more marked as the studies progressed. The chief findings were: (1) The death rate from all causes was greater in persons who used tobacco, especially cigarettes, than in nonsmokers; (2) the greatest increase for smokers, especially of cigarettes, in the risk of developing a disease was for bronchogenic carcinoma, and (3) this increased risk was directly related to the total consumption of cigarettes per day.

It is important to note that the association of cigarette smoking to lung cancer is of a very high order of magnitude Thus, in all three studies there was an increase in the mortality rate among cigarette smokers from all causes of death combined. This excess in the Hammond-Horn study was 68 per cent; i e , the ratio of deaths among men who never smoked to deaths among men who smoked cigarettes regularly was 1 to 1 68 There were, in

evoke carcinomas in mice first painted with subeffective doses of known polycyclic carcinogens (Gellhorn).

Bronchogenic epidermoid carcinoma has not been produced in animals exposed to cigarette smoke, as of the time of this essay. Leuchtenberger et al have described hyperplastic and metaplastic changes in the bronchi of mice exposed to tobacco smoke, and similar effects have been reported in the bronchi of dogs following direct contact with tobacco tar. Whether the pulmonary adenomatous tumors of mice are increased in number by tobacco smoke is not clear, the literature contains one clearly negative and one positive experiment

Another important line of research has been directed toward the analysis of the constituents of the complex chemical mixture in tobacco smoke, in order to identify the chemicals that may be involved in the neoplastic reaction Attention was naturally focused on the polycyclic compounds such as the known carcinogen of coal tar, 3,4-benzpyrene. Pyrolysis of many organic materials, including tobacco, will form such compounds, and a number of them have been identified and isolated, including 3,4-benzpyrene, 1,2-benzpyrene, 1,2,5,6-dibenzanthracene, chrysene and 3,4-benzfluoranthracene (Van Duuren) Whether the removal of these chemicals from tobacco smoke, or their precursors in the tobacco leaf, would produce a cigarette that is "safe" for human beings would have to be established by epidemiologic observations on man.

Interpretation

In 1957, a special Study Group examined the scientific evidence on the problem of the effects of tobacco smoking on health, and arrived at the following conclusion: "The sum of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung." Concurrently, there appeared a report of the Medical Research Council of Great Britain which also drew the inference of a causal relationship between smoking and lung cancer A similar viewpoint has now been accepted by responsible health officials of the United States, Great Britain, the Netherlands, Norway and Sweden.

These conclusions do not mean, of course, that smoking is the only cause of lung cancer, or that all problems regarding smoking and lung cancer have been solved.

Since cancer of the lung is a response to a series of stimuli, the determination of relative importance of these causative factors is of great importance. The epidemiologic facts about lung cancer can be summarized as follows:

1 It is more frequent in males than in females, by a ratio of approximately 4 to 6:1

2 It is more frequent in urban than in rural populations, by a ratio of 1.8 to 2.5:1 among males and 1.3 to 1.5:1 among females

3 It is more frequent in some industrial occupations than in the general population, especially among miners in radioactive-bearing ores, chromate workers, asbestos workers, coal gas workers and iron-miners

4 It is more frequent among the lower socio-economic classes than in the general population, by a ratio of approximately 1 4 1 (Cohart)

5 It is more frequent among tobacco smokers than among nonsmokers, by a ratio of approximately 5 1

6 It is more frequent among regular cigarette smokers than among nonsmokers, by a ratio of 10 1 among all male smokers to 60 1 among smokers of over 2 packs per day

Using a national survey of the smoking habits in the United States, an analysis was made to test how closely the known epidemiologic characteristics of lung cancer could be accounted for by a hypothetic assumption that all lung cancer was due to smoking of tobacco (Haenszel and Shimkin). It was found that two features of the distribution of lung cancer deviated from the predicted model: the male-female sex ratio and the urban-rural difference. However, the sex ratio deviated by only 40 per cent, which is almost exactly the same as the male preponderance in mortality from all causes of death at ages over 35. Direct retrospective studies on women also yield data indicating that the striking sex ratio for lung cancer is reduced to approximately 1 female to 1 4 male when adjustment is made for smoking history, and the lung cancer ratio among rural female and male nonsmokers is also of this order (Haenszel et al) For the urban-rural difference, about 60 per cent of the urban excess remains unaccounted for after adjustment for smoking history, indicating factors in addition to smoking in the urban environment

Some estimates can be made regarding the proportion of lung cancer deaths that can be allocated to the known environmental factors Of the 29,000 people in the United States recorded as dying of lung cancer in 1956, 25,000 were males If the rate of lung cancer in rural nonsmokers is approximately 4 per 100,000 for females and 5 per 100,000 for males, about 7,000 of the total deaths were not attributable to known environmental factors Conversely, 22,000 deaths were due to environmental factors, and of these at least 70 per cent, or 15,000, were associated with smoking of tobacco, particularly in the form of cigarettes. The proportion attributable to tobacco smoking would be increased if only epidermoid and anaplastic bronchogenic carcinoma were considered, excluding pulmonary adenocarcinoma

As an external stimulus to neoplastic change in the lung, cigarette smoking, therefore assumes an important, yet far from an exclusive, causal role. What is meant by "cause" here is devoid of semantic and philosophic subtleties it is presumed that if smoking of tobacco, or at least in the form of cigarettes, were discontinued by the population, the lung cancer death rate would be reduced by a minimum of 50 per cent among the younger generations who had not taken up the habit, and to lesser degrees among those who stop smoking

Since there are other causative factors involved, the prediction is valid only if other factors are held constant. It is possible that other carcinogenic stimuli such as increased radioactive atmospheric pollution may in the future more than replace smoking as a cause in the increase of lung cancer. And because neoplastic disease of the lung is a reaction to many causes, preventive public health must consider multifaceted measures. An accelerated program to determine which air pollutants are particularly associated with lung cancer is essential To embark on a campaign of reducing cigarette smoking and to neglect atmospheric pollution and further research would be an obviously incomplete approach. The obverse, however, is also not reasonable: it is not necessary or desirable to postpone some obvious public health steps in regard to the smoking problem until all aspects of atmospheric pollution are clarified, or until we understand the factors involved in the important residual of lung cancer for which we have no plausible environmental relationship at present. Such steps certainly include education of the public, particularly by the medical profession, regarding the fact that tobacco smoking is a health hazard, setting of the nonsmoking example by public figures that have gained the influence of emulation by young people, and control of the hucksterism for cigarettes over public media of communication

The ubiquitous distribution of lung cancer in human and animal populations indicates that the basic cause of cancer of the lung is widely distributed. Whether the characteristic is distributed at random throughout the population, as would be expected if the disease is due to somatic mutation, or involves an unidentified subpopulation of susceptibles or infected individuals, such as would be expected if cancer is a result of a virus infestation, is of course no better known for bronchogenic carcinoma than it is for any other type of neoplastic disease. Research in these fundamental cell and tissue processes undoubtedly will lead us to better understanding of the neoplastic transformation The knowledge on the epidemiology and pathogenesis of bronchogenic cancer in man that has already accumulated, however, makes this one of the few visceral neoplastic entities in which research and public health can join hands with the victory of substantial prevention being an assured, achievable goal

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CHAPTER 2

Experimental Lung Cancer

By MARVIN KUSCHNER, M.D

THE NOW CONVINCING EVIDENCE for the relationship between exposure to environmental carcinogens and the development of lung cancer was originally derived from epidemiologic studies. It has become increasingly important to supplement these data by experimental induction of pulmonary tumors This necessity relates to the fact that most materials to which man is exposed are complex mixtures, and the identification of specific carcinogens in such mixtures can most efficiently be performed in the laboratory Test systems in which animals are made to develop lung cancer permit the detailed analysis of modes of pathogenesis, of dose response relationships and of the combined effects of selected materials, some of which may contribute to carcinogenesis by nonspecific actions Furthermore, although some materials strongly suspected of being pulmonary carcinogens in humans have been shown to be carcinogenic at other sites in animals[6, 12, 19] some questions have arisen as to the comparability of such effects to those produced in bronchial epithelium

THE DEVELOPMENT OF TEST TECHNICS

Many of the experimental studies relating to pulmonary tumor induction in animals have concerned themselves with pulmonary adenomata in mice Detailed studies of the histogenesis of this tumor by Grady and Stewart[5] and by Mostofi and Larsen[11] have indicated that this tumor arises as a proliferation of lining cells in peripheral alveoli Extensive reviews by Smith,[15] Stewart,[16] and Shimkin[14] have all emphasized the peculiar character of adenoma in mice and its dissimilarity to the vast majority of human lung cancers The common lung tumor in man is a squamous cell or undifferentiated carcinoma arising in a segmental, lobar or main bronchus

Attempts to induce lung tumors in animals comparable to those seen in humans began with the use of polycyclic hydrocarbons known to be highly carcinogenic at other sites. The many failures that attended these early efforts are thoroughly reviewed by Smith[15] The first successful induction of squamous cell carcinoma in experimental animals was reported by Andervont in 1937[1] The technic involved passing threads impregnated



Fig 1—Squamous cell carcinoma of mouse lung induced by transfixion of the lung by a thread *impregnated with 1,2,5,6 dibenzanthracene The tumor extends to and involves* the lateral chest wall Hematoxylin-eosin 200 ×

with 1,2,5,6 dibenzanthracene through the intact chest wall of mice Modifications of this thread transfixation technic in mice and in rats have been described from this laboratory[7] and have resulted in the induction of bronchogenic carcinoma in these species on exposure to methylcholanthrene, 1,2,5,6 dibenzanthracene and 3,4 benzpyrene. Tumors so induced have been well differentiated squamous cell carcinomas which extensively *invade the lung and chest wall (figs. 1 and 2), and occasionally give rise to* metastatic tumor at distant sites, notably the hilar lymph nodes and kidney (fig. 3). Several of the tumors so induced have been transplanted in homologous animals (fig 4)

In order to conveniently study the serial events that precede the development of cancer, another technic has been devised which affords selective exposure of a well defined area of bronchial mucosa to carcinogenic material This involves the implantation within a bronchus of the rat of a cylindrical wire mesh pellet impregnated with test material.[7] Such treatment utilizing methylcholanthrene, 1,2,5,6 dibenzanthracene and 3,4 benzpyrene has again resulted in the production of squamous cell cancers (fig. 5). Preliminary observations of the effects of such implantation on the mucosa would seem to indicate that there is an initial striking hyperplastic *response with evidences of rapid proliferation This is succeeded by meta*plasia to a mature well differentiated squamous epithelium which remains static for relatively long periods of time. Carcinomatous transformation of this epidermoid lining with invasion then rapidly supervenes.



Fig 2—Squamous cell carcinoma of rat lung induced by transfixion of the lung by a thread impregnated with methylcholanthrene Hematoxylin-eosin 200 ×

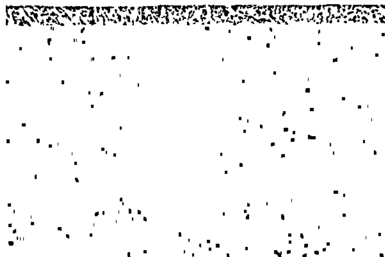


Fig 3—Carcinoma in kidney secondary to carcinoma of the rat lung induced by transfixion of the lung by a thread impregnated with methylcholanthrene The tumor in the kidney consists of nodules of fairly well differentiated squamous cell carcinoma as does the pulmonary primary site The centers of the nests of tumor are keratinized Hematoxylin-eosin 200 ×



Fig 4—Growth of squamous cell carcinoma in the subcutaneous tissue of the groin of a mouse following transplantation from a 1,2,5,6 dibenzanthracene thread induced tumor in a mouse Hematoxylin-eosin 200 ×

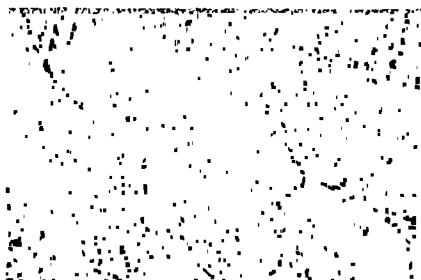


Fig 5—Mucosal origin of squamous cell carcinoma in a rat arising at the site of impaction of a methylcholanthrene impregnated wire mesh pellet Hematoxylin-eosin 225 ×

An additional technic for limited exposure of a selected area of mucosa which allows for direct visual observation of changes and permits of serial biopsy sampling of such an area has been developed in the dog.[13] This technic involves the establishment of a permanent tracheostomy through

which the animals may be repeatedly bronchoscoped with endoscopic application of test material to the bronchial mucosa and biopsy of the treated zones

All of the above described methods for exposing animals to potent carcinogens require operative and manipulative technics which are quite unlike the naturally occurring exposure of the respiratory tract to inhaled materials Attempts to induce tumors in animals by the somewhat less artificial means of intratracheal instillation or by aerosol exposure to polycyclic hydrocarbons have been entirely unsuccessful[7] or have been attended by a much less impressive tumor yield[4] They have been somewhat more productive in the exposure of animals to what would appear to be a much more potent type of carcinogen, ionizing radiation[3, 10, 17]

The contrast between the high tumor yield of such technics as thread transfixion and pellet implantation and the difficulties in producing tumors by inhalation and intratracheal instillation would seem to have important implications in terms of the pathogenesis of lung tumors These two types of exposure differ fron one another in two major respects The first difference is in the level of dosage which is much higher with the transfixion and implantation methods The large quantities of test material contained in the thread or pellet are held there and subject the epithelium to prolonged, continual dosage at a high level In contrast, fluorescent microscopic studies and quantitative chemical determinations of the amounts of methylcholanthrene in the lung after inhalation or intratracheal injection have indicated that there is a rapid disappearance of this material.[7] To render these latter technics successful then, significant prolongation of exposure time and exposure period may be necessary

The second difference between the successful and relatively unsuccessful technics is that the former are all, in varying degree, traumatic procedures Such trauma may produce alterations in the bronchial mucosa which render it more susceptible to the actions of carcinogens One may well speculate that the regenerating epithelium after trauma furnishes a more suitable substrate for carcinogenic activity or that the altered mucosa without its protective coat of watery mucus may be more easily penetrated by carcinogens Further, an area of traumatically induced mucosal alteration may interfere with normal bronchial clearing mechanisms with resulting stasis and accumulation of foreign material and a selective increase in local dosage. These observations may prove particularly significant in the evaluation of the importance of the nonspecific irritative action of certain materials or mixtures of materials in the development of lung cancer They bear, too, on the possible role of pre-existing pulmonary disease in increasing susceptibility to inhaled carcinogenic agents

Examination of Specific Materials Suspected of Being Carcinogenic for Man

The development of the technics described above has furnished the means of examining the carcinogenetic properties of materials implicated in the causation of human lung cancer. The difficulties involved in the induction of experimental tumors with pure polycyclic hydrocarbons, which must be considered much more potent than naturally occurring substances, provide some insight into the failure of attempts to induce animal tumors with such materials as tobacco smoke[9] or compounds of chromium[2] administered by inhalation. It is pertinent to note that for ionizing radiation, the most potent pulmonary carcinogen to which man has been exposed and one in which the tumor incidence was roughly 50 per cent, the average exposure period was 17 years.[18]

As might have been predicted on the basis of human experience, ionizing radiation with its extremely high carcinogenic potency has been the first material to yield significant results when tested in animals. The application of the pellet implantation technic utilizing pellets plated with a radioactive isotope, Ruthenium-106 has proved particularly advantageous[8] (fig 6). It has provided a means for fairly exact calculation of dose to a well defined area of bronchial mucosa Tumor incidences have demonstrated a characteristic dose dependence and the tumor inducing levels have been quite comparable to those calculated for man



... of the lung in a rat This squamous cell tumor ... a platinum pellet plated with 7 microcuries

It seems reasonable to expect that experimental technics will succeed, when properly applied, in isolating, identifying and quantitating specific human carcinogens as well as other agents that may promote carcinogenesis Such findings will offer a basis for rational control of environmental hazards. Negative results to date, as they relate to materials for which there is strong epidemiologic evidence of causal relationship, must be critically interpreted in terms of the difficulties involved in experimental tumor induction with pure potent carcinogenic materials

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CHAPTER 3

Pathogenesis of Carcinoma of the Lung

By ARTHUR PURDY STOUT, M D

THE ONLY CARCINOMA TYPE about the pathogenesis of which anything definite is known is the squamous cell carcinoma developing from the bronchial mucosa So far as I am aware the precancerous process leading to the development of adenocarcinoma is actually unknown Since 1 out of 10 bronchial adenomas are said to metastasize, it might be argued that the other 9 should be regarded as potentially precancerous, but there is no proof that the occasional malignant adenoma originated from a benign adenoma The rare bronchiolar carcinoma which consists of a proliferation of mucus-secreting glandular structures presumed to be derived from the epithelium of terminal bronchioles is supposed by some (Laipply et al.) to have a benign adenomatous phase, but the majority of observers believe that they are all forms of carcinoma albeit a variety that is slow to metastasize (Overholt et al). For the great majority of adenocarcinomas, however, a precancerous phase is entirely unknown.

A great deal of investigative work has been done on the possibility of the occurrence and recognition of precancerous phases for squamous cell carcinoma in the bronchi It was inevitable that this should be so because of the recognition of definite precancerous lesions in the skin and in other mucous membranes notably the cervix uteri, the vulva and vagina, the oral cavity and the larynx It is of great interest that precancerous lesions in these different foci that lead to the development of invasive squamous cell carcinoma are often quite different and any attempt to apply criteria pertaining to precancerous phenomena in one part of the body to another part may lead to completely erroneous conclusions. For example, leukoplakia with squamous hyperplasia in the oral cavity and the vulva is justifiably regarded as a precancerous lesion. But in the cervical canal, and at the squamoglandular junction in the external os, squamous metaplasia is not regarded as a precancerous lesion.

When the tracheobronchial tree is studied certain lesions are observed which might be precancerous One of these is a proliferation of the basal layer of cells called basal hyperplasia This can vary in amount very greatly It is natural to investigate the possible relationship to carcinoma of any marked proliferative activity on the part of cells of the surface mucosa

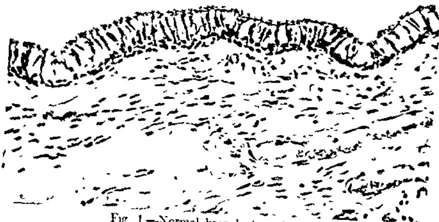


Fig 1—Normal bronchial epithelium



Fig 2—Modern basal cell hyperplasia.



Fig 3—Atypical basal cell hyperplasia

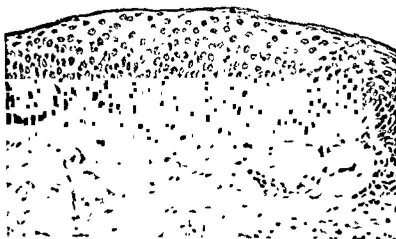


Fig 4—Squamous metaplasia



Fig 5—Carcinoma-in-situ

There is no proof as yet that this basal hyperplasia has significance as a precancerous process. Another change, which has been frequently noted, has been called stratification This means that the surface mucus-secreting, ciliated cells disappear and are replaced by flattened cells while the deeper cells retain their orderly arrangement. None of the altered cells is anaplastic and so far there has been no proof that stratification is a precancerous lesion

Very possibly stratification is a change that may precede the next lesion to be described which is squamous metaplasia In this interesting and quite common change in the tracheobronchial tree the surface mucosa loses all its normal characteristics and becomes converted into a membrane of squamous epithelium It must be emphasized, however, that while the change from normal epithelium to a squamous membrane is striking, none of the altered cells has the characteristics of a cancer cell. Since leukoplakia is a precancerous lesion in the vulva and oral cavity and since the large majority of carcinomas of the bronchi are squamous cell cancers, squamous cell metaplasia in the tracheobronchial tree might be supposed to be a precancerous lesion there. However, when it is realized that squamous metaplasia regularly follows severe inflammation of the tracheobronchial tree that causes ulceration or fistula formation probably as part of the process of repair and mucosal regeneration, it will be appreciated that squamous

metaplasia due to inflammation is not a precancerous lesion. It is regularly found at autopsy, for example, in the tracheobronchial trees of children with severe ulcerative bronchitis Except as a curious phenomenon, children and young adults do not develop bronchial carcinomas This is not to say that carcinoma never develops in squamous metaplasia, for on rare occasions anaplastic carcinoma cells may be found in an area of squamous metaplasia in which case one must interpret such a lesion as carcinoma *in situ*, but this is a rare phenomenon.

The only lesion in the tracheobronchial mucosa which can be regarded definitely as being a true forerunner of invasive carcinoma is the so-called carcinoma *in situ*. This term should be used only when the normal surface mucosa is entirely replaced by anaplastic cells entirely comparable to the cells found in invasive carcinoma Such cells will vary in relative size with the formation of small giant forms, most of the nuclei will have clearly defined nuclear markings with large nucleoli and not infrequently mitoses These changes may extend down the ducts of the mucous glands, but of course there will be no disruption of the basement membrane and extension of the tumor cells into the substantia propria for if that occurs the carcinoma is no longer *in situ*, but has become invasive. Studies of the tracheobronchial trees in cases where there is gross invasive carcinoma of the bronchi have shown that patches of carcinoma *in situ* are often present in both lungs Occasionally, it has been possible to demonstrate microscopic invasive carcinoma from foci of carcinoma *in situ* in these cases so that these lesions can be regarded justifiably as truly preinvasive carcinoma There is good evidence that carcinoma *in situ* is frequently found in individuals who are known to have inspired carcinogens over a long period of years

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CHAPTER 4

Pathology of Carcinoma of the Lung

By OSCAR AUERBACH, M D.

MALIGNANT EPITHELIAL TUMORS OF THE LUNG may be divided into two main groups: (1) carcinoma of the bronchus and (2) pulmonary adenomatosis. There are also two unusual variants of bronchial carcinoma, namely microscopic carcinoma and giant cell carcinoma Carcinoma of the bronchus forms over 95 per cent of the observed cases.

CARCINOMA OF THE BRONCHUS

Determining the location of the origin of the cancer within the bronchus is beset with difficulties We feel that at times it is impossible to determine the site of origin with complete accuracy In cases where the carcinoma involves the main bronchus there is often a contiguous involvement of a portion of the adjoining trachea and the neighboring branch bronchi. These cases are classified as having their origin in the major bronchus with contiguous extension to the trachea and neighboring bronchi

The right lung is involved slightly more frequently than the left The main bronchi are most often the site of cancer, followed by the upper lobes The lower lobes are much less frequently affected than those in the upper lobes

When the tumors are measurable they vary in size from 2 0 to 20 0 cm. The majority of these vary in size from 5 0 to 10 0 cm

Pathologic Anatomy

Classifications based on the gross appearance of carcinoma of the bronchus have been extremely varied We have found that this may be divided into three main groups (1) the hilar type arising from the right or left main bronchus, (2) the pulmonary type arising in bronchi within the lung parenchyma and (3) the peripheral type in which no bronchial origin can be found on gross examination

In the first two groups inflammatory changes in the lung parenchyma beyond the obstruction dominate the clinical picture early in the course of the disease

Hilar Type: About 60 per cent of the cases of bronchial carcinoma occur in this group The main involvement in this form is within the right or left major bronchi There is often a contiguous involvement of the trachea

and neighboring branch bronchi. Occasionally, there is also a contiguous involvement of a small part of the major bronchus of the opposite lung.

The earliest changes are those of a thickening, roughening and granularity of the mucous membrane with a loss of normal architecture. At this stage of development a definite diagnosis can be made only by microscopic study. As the process continues more of the surface is involved. There is also an extension of the tumor through the wall with a complete disruption of the normal architecture of the bronchus. Having reached the outer wall of the bronchus, the tumor extends into the adjoining mediastinal structures. First, the superior and inferior tracheobronchial lymph nodes are encircled by the tumor and gradually replaced by it. The malignant growth has a gray or yellow-white appearance which is of firm consistency containing yellow areas of necrosis. The tumor then extends to the neighboring structures to involve the medial pleura of the affected side. The recurrent laryngeal and phrenic nerves lying on the lateral aspect of the trachea may also become embedded in the tumor mass. In its anterior extension the carcinoma encircles the walls of the pulmonary artery and vein, the superior

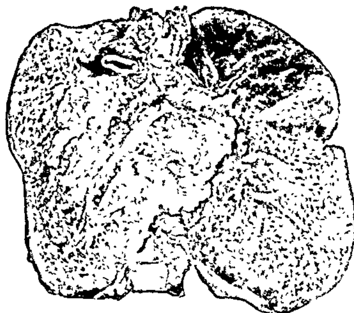


Fig. 1—Carcinoma of the bronchus—hilar type. Carcinoma which has arisen in the left main bronchus has resulted in a wide mediastinal mass. Note the greatly shrunken fibrotic left lung.

vena cava and the arch of the aorta, the parietal pericardium and, less frequently, the myocardium

Obstruction of the superior vena cava occurs much more frequently when the tumor arises in the right main bronchus. Luminal obliteration in most instances is due to a compression of the tumor mass which surrounds and invades the vessel wall. Less frequently, there is obliteration by the extension of the tumor into the lumen of the vessel or the formation of a thrombus in the narrowed lumen.

The tumor grows outward in a radiating, fan-shaped manner, is usually of firm consistency and has a yellow color A coronal section of the mediastinum shows remnants of the lymph nodes and the blood vessels compressed within the tumor mass. In its posterior progression, which is a less frequent occurrence, the carcinoma may extend into the wall of the esophagus. In rare instances the tumor perforates into the lumen of the esophagus.

The lumen of the bronchus becomes progressively narrower, rarely because of a fungating mass growing into the lumen, but far more frequently because of the extensive thickening of the bronchial wall in the region of the tumor As the tumor mass grows larger it undergoes necrosis Toward the lumen the necrotic material is liquefied so that parts of the tumor are expectorated and the lumen regains some of its patency.

The retention of bacteria distal to the narrowed portion of the bronchus results in suppurative bronchitis, bronchopneumonia, lung abscess, bronchiectasis and pulmonary fibrosis. As the process continues the affected lung parenchyma becomes contracted and is firm and gray or brown with an extensive thickening of the overlying pleura. Occasionally, the lung abscess may rupture into the pleural space and result in a bronchopleural fistula and an empyema. Secondary infections of the lung and their sequelae dominate the process and so obscure the primary lesion that the diagnosis of lung abscess or empyema is made before the discovery of the malignant tumor It is these complications and sequelae which are responsible for many deaths.

Pulmonary Type. About 25 per cent of the cases of bronchial carcinoma fall into this group. The gross findings in different cases of this group vary but slightly, and such differences as occur depend on the order of the bronchus in which the carcinoma arises

The early anatomic changes are similar to those in the hilar type In its growth outward, the tumor encloses the regional peribronchial lymph nodes and extends into the surrounding lung parenchyma. This forms a large yellow area and in cases arising in the first order bronchi the mass extends to the pleura, usually in the medial aspect of the lobe, and from there to the mediastinal structures. The mediastinal invasion is never as extensive as in the hilar type. However, some authors have included these cases in their hilar group

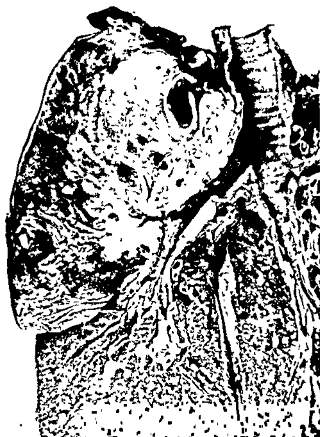


FIG 2—Carcinoma of the bronchus, pulmonary type Carcinoma which has arisen in the left upper lobe bronchus has extended through the wall into the surrounding lung parenchyma and the left superior tracheobronchial angle Note the greatly contracted lung beyond the involved bronchus

As the tumor grows, areas of necrosis and occasionally liquefaction develop within it. In those cases where liquefaction occurs, evacuation of the liquefied material results in a cavity The cavity in very occasional instances is lined by irregular, necrotic tumor fragments and when this occurs the tumor is most frequently a squamous cell carcinoma Much more frequently, however, the cavity is lined by a dirty gray membrane indicating a secondary infection Occasionally, a branch of the pulmonary artery may be invaded by the tumor Erosion of the wall of the artery as it lies in the lumen of the cavity will result in a fatal hemorrhage. Fatal hemorrhage occurs in from 1 to 3 per cent of carcinomas of the bronchus

Concomitant with the obstructive changes in the lumen of the bronchus



Fig 3—Carcinoma of an upper lobe bronchus showing narrowing of its lumen with peribronchial extension More recent involvement of the main bronchus shows roughening, thickening and granularity of the mucous membrane with a loss of the normal architecture.

are the inflammatory changes which develop in portions of the lung parenchyma peripheral to the occlusion. These changes are usually limited to the segment supplied by the involved bronchus. With the extension of the tumor into adjoining proximal branches other segments will show these secondary changes Occasionally, the tumor of a first order bronchus may extend to the bronchus of an adjoining lobe, and with obstruction this lobe will also develop the extensive secondary infection.

The abscess cavities are easily distinguishable from the tumor cavities. The former are lined by a dirty gray membrane and show no tumor tissue within their walls.

Peripheral Type This is present in about 15 per cent of the cases of bronchial carcinoma. This type of tumor offers the greatest diagnostic difficulties. Although this tumor appears in most classifications, its criteria are not sharply defined.



Fig 4—Lung abscess of the right upper lobe distal to a carcinoma of the bronchus

The tumor is present in the peripheral portions of the lung and is of variable size, generally from 2 0 to 10 0 cm. It is usually a circumscribed growth in which the origin almost always has not been traced to a grossly visible bronchus Occasionally, the tumor lies completely within the lung parenchyma and is an incidental finding at autopsy In others, it may extend to involve the overlying pleura and sometimes it may extend into the adjoining chest wall. We have observed a peripheral carcinoma located in the superior and medial aspects of the lobe which extended into the mediastinum to involve the pericardium and the myocardium of the heart.

Changes in the Pleura Extensive pleural involvement may occur in all three forms of bronchial carcinoma. Most often, however, the carcinomatous involvement of the pleura is limited to the area where the underlying tumor reaches the surface Occasionally, it may spread over the pleural surface covering the entire lung encasing it with carcinomatous tissue (carcinoma en cuirasse) This is sometimes mistaken for a mesothelioma.

In many instances the changes in the pleura are noncancerous in character Most often they are a reaction to the inflammatory processes in the



Fig 5—Bronchial carcinoma, peripheral type The tumor is confined to the lung parenchyma

underlying lung parenchyma. In the early stages, the pleural cavity contains a serous or fibrinous exudate Later, as a result of the organization of this exudate, the pleurae become thickened and the pleural space is obliterated When pulmonary abscesses which developed beyond the obstructed bronchi perforate into the pleural space, suppurative pleuritis develops with a resultant thickening of visceral and parietal leaves.

Histopathology

We have found that all the cases of bronchial carcinoma can be classified into one of three types: squamous cell, undifferentiated (oat cell) carcinoma and adenocarcinoma The first two types form the great majority of cases Squamous cell carcinoma is the most frequent type observed.

We have not been able to verify a view expressed by several authors that the squamous cell carcinoma more commonly arises in the hilar region and is more common after the age of 50 years and that before the age of 50



Fig 6—Extensive pleural involvement (carcinoma en cuirasse) secondary to bronchial carcinoma

the undifferentiated cell type predominates. Morphology has nothing to do with the bronchial level of origin and that none of the three types is found exclusively in one location

There is perhaps no tumor which is so pleomorphic as carcinoma of the lung It varies from the most undifferentiated to the most fully differentiated forms

Squamous Cell Carcinoma We have included in this group all the tumors which have a sheetlike arrangement The best differentiated tumors resemble those of the skin and show evidence of keratinization with epithelial pearls The tumor cells are arranged in compact masses, sheets or cords and may contain fine or coarse strands of keratin The cells are tightly packed and their cytoplasm is abundant Such well differentiated carcinomas are in the minority The majority of squamous cell carcinomas,



Fig 7—Recurrence of tumor following right pneumonectomy

while they maintain these general characteristics, show little or no keratinization Some carcinomas which are well differentiated in some areas, show in others anaplastic zones. Some of these anaplastic areas may show small multinucleated tumor giant cells Squamous cell carcinomas sometimes show areas of glandular formation

In contrast to the views of some we have applied the term poorly differentiated squamous cell carcinoma when there is no evidence of epidermidization, namely the production of keratin, cornified epithelium or prickle cells Tumors lacking these features, but showing a sheetlike ar-

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posed of small cells having no organoid pattern. The cells grow in loose or compact alveolar nests which are separated by dense bands of con-



Fig 8—Tumor extension into the lumen of the superior vena cava following a carcinoma of the bronchus

nective tissue Delicate connective tissue extends among and between the individual groups of cells The cells contain a deeply stained nucleus with a reticular pattern and a scanty basophilic cytoplasm. Nucleoli are small, but multiple and prominent The cells often have a spindle-shaped appearance which may show nuclear palisading often in perivascular position Small giant cells with overlapping of the nuclei may also be seen Mitotic figures are frequent with areas of necrosis prominent in the tumor.

Adenocarcinoma Pure glandular carcinomas are very infrequent The tumor is characterized by cells which form glands or produce secretion There are definite acinous and papillary structures In the poorly differentiated types the tumor may have a pleomorphic nature in which well formed acini cannot be demonstrated in every microscopic section Intracellular or extracellular mucus may be observed in some cases. Frequently, squamous elements can be found in the tumor Lymphatic and venous invasion is often observed and accounts for the frequent and wide-spread metastases occurring in this type of tumor Adenocarcinomas may sometimes show areas of squamous metaplasia



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Undifferentiated Carcinoma (Oat Cell): This is an anaplastic group referred to as the "round or small cell carcinoma." The carcinoma is composed of small cells having no organoid pattern. The cells grow in loose or compact alveolar nests which are separated by dense bands of con-



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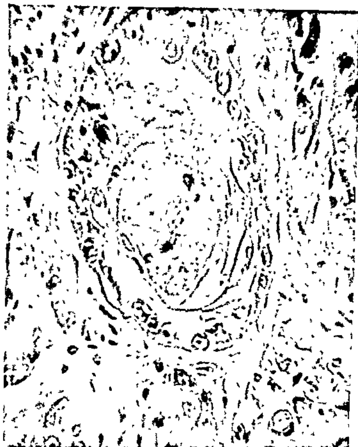


Fig 9—Well differentiated squamous cell carcinoma of the bronchus

Metastases

Widespread metastases as a result of lymphatic and blood stream invasion are frequently encountered in bronchial carcinoma Occasionally, small tumors may result in widespread blood stream metastases Sometimes, tumors attain very large size without producing remote metastases.

Regional lymph node metastasis is present in over 90 per cent of the cases of carcinoma of the lung When metastases do not occur, they are more frequent in cases of peripheral carcinoma of the lung.

Bronchial carcinoma although it metastasizes to many organs, shows a predisposition to seed in the brain, adrenals, bones, kidneys and liver. These organs are involved in about one-third of the cases.

It has been said that the more anaplastic tumors show a great tendency to widespread metastases while the squamous cell carcinoma tends to remain limited to the regional lymph nodes. Our own findings would indicate that some of the most anaplastic tumors may remain confined to the re-

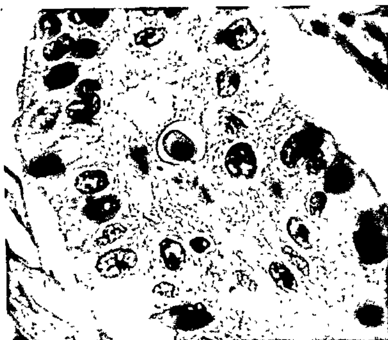


Fig 10—Poorly differentiated (large cell) carcinoma of the bronchus

gional lymph nodes, while some of the most differentiated may become widely disseminated. We have found that in 57 per cent of the undifferentiated cell carcinomas and in only 17 per cent of the squamous cell carcinomas, there were extrathoracic metastases

The presence of distant metastases in 75 per cent of the cases of adenocarcinoma would tend to verify the view that this is the most rapidly growing and widely metastasizing of lung tumors

Alveolar Cell Carcinoma (Pulmonary Adenomatosis-Bronchiolar Carcinoma)

This tumor, which was first described in 1876, has received much prominence in the past decade Although a few authors attempt to divide this entity into benign (pulmonary adenomatosis) and malignant (alveolar cell carcinoma) forms, there is now general agreement that the process is one entity. The reason for this is that transitional forms have been shown to exist, and there are no reliable histologic criteria that serve to distinguish tumors that are localized to the lung from those that have metastasized. These tumors usually produce death by their local effects on the pulmonary parenchyma rather than by metastases

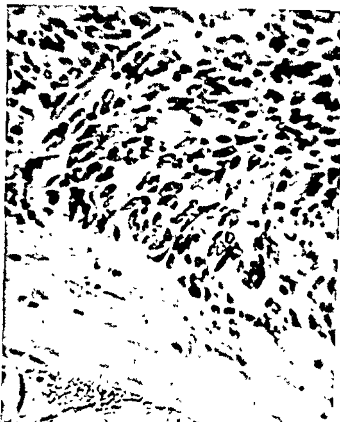


Fig 11—Undifferentiated (oat cell, small cell) carcinoma of the bronchus

There are two views as to the histogenesis of this process. One is that the tumor arises from the alveolar cells and the other is that the bronchiolar cells are the source of origin. Speaking for bronchiolar origin is the replacement of portions of the bronchiolar lining by the tumor cells. The neoplastic tissue then grows out on the supporting interalveolar septa.

In recent years there has been some skepticism expressed as to whether this entity is not a primary pulmonary tumor but a metastatic lesion. Our own experience is that complete autopsies have shown that this is a distinct entity and must be accepted as such

Pathology

There are two forms distinguishable, the multiple nodular type and a diffuse form In both forms the lungs are firm and voluminous and do not collapse The lungs are often increased in weight up to 2,800 Gm. In the nodular form there are many discrete and confluent yellow-gray, pink or white tumor foci which vary in size from 1.0 mm to 1 0 cm. or more which are widely scattered throughout both lungs The foci are globular and of



Fig 12—Adenocarcinoma of the bronchus

firm consistency Some foci have a yellow, necrotic appearance; others may show a mucinous secretion Tumor extension through the lymphatics is seen occasionally as a network of fine strands spreading among the nodules. The pleural surface may also be studded with tumor nodules

The much less frequent diffuse form is characterized by an involvement of a lobe or an entire lung on one or both sides The tumor growth resembles the gray hepatization of lobar pneumonia except that the involved lung tissue is denser than in lobar pneumonia. The cut surface is firm, yellow-white or gray-pink and from it may exude gelatinous or mucoid material. Necrosis is generally not observed on gross examination

Microscopic Both gross types show a similar picture in which the tumor stroma is made up of the slightly thickened alveolar walls Large cuboidal or columnar neoplastic cells in one or more layers line the pulmonary alveoli forming a slightly serrated border Frequently, the cells are thrown into papillary projections. There is little evidence of pleomorphism The

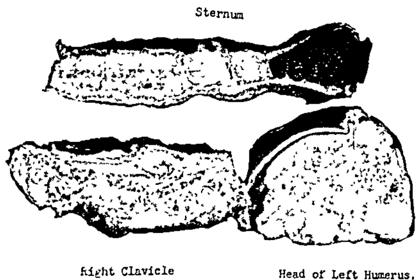


Fig 13—Extensive bone metastases in a case of bronchial carcinoma.



Fig 14—Brain metastasis in a case of bronchial carcinoma.

nuclei are oval or round, some with prominent nucleoli The cells may be bizarre, with basophilic cytoplasm and irregular or multiple nuclei. Occasionally, mitotic figures are present, especially where the bizarre forms exist The alveolar spaces contain desquamated tumor cells, alveolar phagocytes and some neutrophiles. Small nests of tumor cells may be found in lymphatic channels, alveolar septa and also in the pleura When mucus is produced in the cells, the nuclei are basally placed Pools of mucin may be present within the alveolar spaces which, when stained with mucicarmine, have a red appearance

Metastases occur in about one-half of the cases In approximately one-half of those with metastases there is involvement of the regional lymph nodes only Distant metastases occurred in only one-quarter of the cases



Fig 15—Aveolar cell carcinoma of the lung

with involvement of the liver, distant lymph nodes, kidneys, brain, adrenals and pericardium

All extrapulmonary metastases duplicate the alveolar papillary character of the tumor in the lung.

Minute or Microscopic Carcinoma

These cases are only infrequently observed. The diagnosis in most instances is first made on routine microscopic examination. Early invasion *of the lymphatic and venous channels is a striking characteristic finding in these cases. Diligent search is required to find the primary involvement in* the bronchus; the reason for this is the presence of metastases in the pleura and tracheobronchial lymph nodes. Occasionally, brain metastasis may be the only evidence of tumor. The morphologic evidence of a tumor resembling bronchial origin may lead to a successful discovery of the original tumor in the bronchus

Giant Cell Carcinoma

The pattern of distribution of the tumor is essentially that shown of bronchial carcinomas in general. The tumors generally show a peripheral distribution with varying degrees of involvement by extension to the pleural cavity, thoracic wall, diaphragm and pericardium. The majority of the tumors are of a large size which do not penetrate into the surrounding bronchi There are patchy areas of necrosis and hemorrhage The tumors have a fleshy smoothness and homogeneity in texture and color of the cut

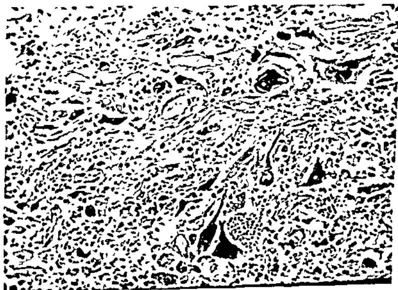


Fig 16—Giant cell carcinoma of the lung

surface. The metastatic lesions show gross characteristics that are generally similar to those of the lung masses

Microscopically, the characteristic feature is the striking prevalence of multinucleated giant cells of wide morphologic variety in the primary and metastatic lesions There is a marked degree of phagocytosis by the tumor cells. Interspersed among them are mononuclear cells that show a pleomorphism in size and shape similar to that of the giant cells In most areas the tumor cells tend to form cords, sheets or sheetlike clusters outlined by delicate vascularized strands of connective tissue. In areas where the cells show a spindle or strap shape it may create the effect of a mesodermal rather than an epithelial growth A careful and thorough analysis of the morphologic criteria is necessary to differentiate this carcinoma from rhabdomyosarcoma or some other sarcoma

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CHAPTER 5

Diagnosis of Bronchogenic Carcinoma—Medical

By SEYMOUR M FARBER, M D, AND WILLIAM MANDEL, M D.

MANY PATIENTS WITH BRONCHOGENIC CARCINOMA are theoretically amenable to surgical procedures, the only presently known treatment that may produce a cure, if undertaken shortly after the onset of symptoms or signs The difference between the possible rate of cure and its actual achievement is in part the result of failure in early diagnosis, though to a greater extent it is the result of the long asymptomatic phase of the disease. There was, perhaps, little point in making an early diagnosis before the time surgical procedures were practical, but even during recent years the lapse of time between the onset of symptoms and the patient's entry into the hospital has remained the same, averaging 6 to 8 months (Nicholson et al.)

Two intervals are involved in delaying the diagnosis (Kutner et al): The first is the period between the onset of symptoms and the visit to the physician; the second is the time before the diagnosis is made by the physician Reduction of the first interval depends on educating the public. Campaigns by cancer control groups have tried to accomplish this, but in general they have not been too effective Reduction of the second interval depends on educating physicians to an awareness of the early and atypical manifestations of the disease The problem of reducing the time required to make a diagnosis is complex For every patient whose initial complaints of cough, sputum, wheeze, malaise, dyspnea or vague chest pains are in reality the early symptoms of bronchogenic carcinoma, there are many others with similar complaints which can be traced to minor respiratory infections or to no detectable disease Furthermore, the latter patients are drawn in large part from the same age group in which bronchogenic carcinomas are apt to occur The physician is reluctant to advise roentgenographic and other diagnostic studies in such cases, and yet, it is only by a high index of suspicion and an overinterpretation of symptoms and signs that the salvage rate will be increased Every adult patient with minor chest complaints not immediately traceable to a known cause should be potentially considered as having bronchogenic carcinoma

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...sease is often

inoperable during the stage of early clinical manifestations, the emphasis on early diagnosis may be wrong. The emphasis perhaps should be placed on detecting the disease in its preclinical period, a more appropriate time for suitable treatment, although the cure rate may be low even at this time (McClure). Currently, the diagnosis is being made in only a small percentage of instances before the onset of symptoms or signs. With the available knowledge, the preclinical diagnosis can best be accomplished by repeated mass surveys, either roentgenographic (Boucot) or cytologic, of the most susceptible population groups, i.e., people, especially men, between 45 and 60, who have been heavy cigarette smokers for many years. The effort is directed to seeking the patient rather than having the patient seek the physician. The problem of the symptomatic patient will still remain; it is here that the physician's awareness of the disease, even though he knows that an early diagnosis does not necessarily mean an early carcinoma, must determine the measures taken toward further evaluation of his patient's complaints.

History and Physical Examination

The difficulties in diagnosing bronchogenic carcinoma arise from the fact that the disease is not manifested by a typical or characteristic symptom complex or by distinctive physical signs. No symptoms or signs may be present or there may be an infinite number and variety which tend to change during the course of the disease. The incidence of major initial symptoms from 4 reported series is presented in table 1, while the symptoms arising during the course of the disease in 4 other series are presented in table 2.

The history and physical examination may suggest not only bronchogenic carcinoma, but other pulmonary diseases, such as bronchitis, influenza, viral

Table 1—*Initial Symptoms of Bronchogenic Carcinoma*

Symptoms	Mason (1949) (1,000 cases) %	Ariel et al (1950) (1 109 cases) %	Taylor and Waterhouse (1950) (1,592 cases) %	La Due (1955) (811 cases) %
Cough	31	21 3	28 7	41 1
Chest Pain	24	24 9	21 9	22 9
Dyspnea	11	7 6	12 8	1 4
Hemoptysis	6 7	5 6	7 7	5 9
Asthenia	9 5	6	3 0	4 1
Respiratory Infections	—	9	2 6	4 9
Wheezing	1 7	1 4	—	—
Weight Loss	3 1	2 6	1 2	3 7
Dysphonia	1 0	1 3	1 8	1 4
Dysphagia	0 6	1 0	0 7	—
Fever and Night Sweats	1 7	0 7	0 4	—
All Other	9 7	20 1	19 2	14 6

TABLE 2—*Symptoms During Course of Bronchogenic Carcinoma*

Symptoms	Reinhoff (1950) (502 cases) %	Bryson and Spencer (1951) (Men—743 cases) %	Bryson and Spencer (1951) (Women—123 cases) %	Farter (1954) (1536 cases) %	Ochsner et al (1957) (442 cases) %
Cough	71	52.6	48.8	67	84
Chest Pain	50	29.6	28.5	43	58
Dyspnea	23	33.1	35.0	42	42
Hemoptysis	63	26.4	8.9	35	51
Asthenia	—	—	—	36	42
Weight Loss	39	35.1	30.9	49	63
Respiratory Infection	18	—	—	—	46
Chills and Fever	13	—	—	—	17
Wheezing	—	—	—	—	14
Dysphonia	—	3.0	0.8	—	4
Dysphagia	—	2.8	6.5	5	2
Metastatic Symptoms	—	36.2	45.5	34	—

and bacterial pneumonias, tuberculosis, bronchiectasis, lung abscess, pulmonary infarction and metastatic lung tumors The malignancy may coexist with other chest diseases Hauser and Glazer reported 10 cases of coexistent pulmonary tuberculosis and bronchogenic carcinoma and reviewed other reported similar cases. In addition, the carcinomatous metastases may simulate disease in other portions of the body, so that the patient may be seen by a variety of specialists before the diagnosis is made. These may include the cardiologist, gastroenterologist, neurologist, orthopedist as well as the general physician and surgeon. A purely clinical diagnosis may be impossible, yet it is mainly by the history and physical examination that the physician first suspects the presence of a bronchogenic carcinoma A strong suspicion is justified if there are unexplained pulmonary symptoms, such as cough, hemoptysis, dyspnea, wheezing, chest pain and repeated respiratory infections, in a patient, particularly a man over the age of 40. Furthermore, if the pulmonary symptoms are associated with extrapulmonary findings, carcinoma of the lung must be considered

Most patients complain initially of symptoms referable to the chest, but many first see the physician because of extrathoracic complaints, the pulmonary symptoms being found incidentally. In some reports, as high as 25 per cent of patients have initial symptoms indicative of inoperability (Paulson and Shaw). The important thing is to focus attention on those symptoms which do not preclude operability, namely, the respiratory symptoms.

Cough and Sputum

A cough, or a change in cough habit, is found in approximately 50 to 80 per cent of patients at some time during the course of the disease, and it is the initial symptom in 20 to 40 per cent of cases The cancers arising *from*

the smaller distal bronchi, which comprise the so-called silent peripheral tumors, may not produce cough for long periods The more centrally located tumors that produce any significant degree of intrabronchial obstruction will invariably cause a cough This is frequently the earliest symptom to appear and the one which usually persists throughout the disease The onset of the cough, which at first may occur only with exertion, is often ignored and may be recalled only with difficulty.

The tumor acts as a foreign body or obstruction within the bronchus, and the cough, which arises by stimulation of the respiratory tract mucosa, represents the effort to expel it At first the cough is dry and spasmodic and produces little or no sputum When the cough fails to remove the foreign body, thin watery mucus is secreted as if an attempt were being made to wash the tumor out At this stage the cough produces a small amount of sputum and is often considered a "cigarette cough," but it is characteristically more paroxysmal in nature

The intrabronchial tumor may obstruct drainage of bronchial secretions, and the sputum becomes gray and mucoid Shortly after secretions begin to collect, however, some degree of parenchymal infection develops, or the tumor itself undergoes necrosis and becomes infected When the obstruction is incomplete, the infection is apt to present as mild, repeated pulmonary infections which the patient and physician may ascribe to the "flu," or to "virus pneumonia" With infection, the sputum tends to become mucopurulent Unless the infection is treated with antimicrobial drugs, either self-administered or given by a physician, the sputum will become purulent and copious in amount Nothing therefore is characteristic of the sputum, for it may vary from a clear expectoration to a foul purulent discharge, or it may be scanty or copious in amount If the tumor progresses to complete bronchial obstruction, the cough and sputum may disappear temporarily, but there are periods when the obstruction is relieved and sputum is again raised in copious amounts The so-called alveolar cell carcinoma, a bronchogenic carcinoma arising from the terminal bronchioles, is often characterized by the expectoration of large quantities of frothy and mucoid sputum

Many patients will first come to the physician because of an acute respiratory infection which has failed to clear or because of repeated episodes of pneumonitis The history may reveal that the patient has a persistent cough *or a change in cough habit that does not respond to the usual remedies* A cough of this type must be suspected by physician as possibly arising from an obstructed bronchus

Chest Pain

Chest pain, the second most common respiratory symptom of bronchogenic carcinoma, occurs in approximately 30 to 60 per cent of patients at

some stage in the course of the disease. As an initial symptom, it has been reported to occur in from 20 to 30 per cent of cases. Such pain does not necessarily indicate an inoperable tumor. In the earlier stages, the chest pain is often not too severe; most patients describe it as an annoying or dragging sensation The pain is usually felt as a persistent ache unrelated to cough or respiratory movement and is commonly experienced on the side on which the tumor is located, although it may be referred to the neck, back or abdomen This type of pain is caused either by local compression of a larger bronchus with ulceration and spasm of the mucosa or by invasion of the pulmonary blood vessels, the parietal pleura, the mediastinal structures, the trachea or the thoracic wall. Pain may also follow involvement of these structures by infection secondary to the tumor. Occasionally, there are spontaneous remissions of the pain Ballantyne, Clagett and McDonald have reported instances of chest pain simulating myocardial infarction that they believed could result from peripheral pulmonary infarction or thrombosis in pulmonary vessels invaded by tumor.

At some stage of the disease, a typical sharp and severe pleuritic pain, accentuated by deep breathing or coughing, may occur. This pain does not necessarily indicate pleural metastases as it may be the result of secondary inflammatory pleural changes. The pain may disappear with the onset of a pleural effusion and may reappear after thoracentesis.

Severe, constant and progressive chest pain often occurs in advanced stages of the disease. The patient may describe it as sharp, boring and knifelike, and the physician finds it difficult to alleviate. This type of pain suggests extrapulmonary involvement, either of the pleura, chest wall or mediastinum Mediastinal involvement is also suggested by a sharp, constant, dull pain referred to the back

Dyspnea

Dyspnea is common during the course of bronchogenic carcinoma, occurring in about 30 to 40 per cent of cases It is the result of varying degrees of bronchial obstruction, infection and invasion of parenchyma leading to nonfunctioning lung and blood shunting around this region. In general, the symptom is neither prominent nor severe. There is no consistent correlation between the degree of dyspnea and the amount of lung tissue involved, for the symptom has been observed in association with small and uncomplicated growths

Occasionally, a severe attack of dyspnea develops in patients with bronchogenic carcinoma This may follow the onset of atelectasis, pleural effusion or lobar pneumonia. When severe dyspnea develops without evidence of pneumonia or pleural effusion, it is usually the result of occlusion of a major bronchus, leading to atelectasis The dyspnea has been known to re-

sult from pressure on the trachea by carcinomatous mediastinal lymph nodes.

Hemoptysis

Hemoptysis, a most fortunate symptom since it is not likely to be disregarded, may occur in the form of occasional expectoration of small amounts of bright red blood, as frank hemorrhage or as blood-streaked sputum. The last type, which is by far the most common, is caused by ulceration and erosion of the bronchial mucosa by the tumor with involvement of the capillary and venous vessels. The hemoptysis may recur and is often aggravated by coughing An estimated 25 per cent of patients over the age of 40 who have hemoptysis have bronchogenic carcinoma, bronchiectasis is the only commoner cause

Hemoptysis is the initial symptom of bronchogenic carcinoma in about 5 per cent of instances It occurs as blood-streaked sputum, scanty in amount, in some 35 to 60 per cent of patients during the course of disease. The hemoptysis is frequently related to the presence of infection, and as tumors in the distal portions of the respiratory tree become infected later than those in more proximal regions, the distally located tumors are less apt to cause hemoptysis Irradiation may cause necrosis of vessel walls and so predispose to hemoptysis Hemoptysis occurs more commonly in cases of squamous cell carcinoma, probably because of its location in the main, lobar and segmental bronchi and its slower rate of growth, than in other types of bronchogenic carcinoma This tendency is partially responsible for the more favorable prognosis in cases with this tumor type, since bloody sputum is not likely to be neglected, and an earlier diagnosis can be made When pure blood is expectorated, it suggests an undifferentiated carcinoma or, even more likely, an adenocarcinoma Massive and fatal bleeding from the lung rarely is caused by bronchogenic carcinoma

General Symptoms

In addition to the local manifestations from the tumor, systemic effects such as weight loss, cachexia, weakness, anorexia, fatigue and noctridosis may be observed These effects result from absorption of toxic products from ulcerated or necrotic tumor tissue or from secondary bacterial infection of pulmonary tissue in association with pneumonia, bronchiectasis, lung abscess, pleurisy and empyema These symptoms are suggestive but not conclusive evidence of an advanced stage of the disease

Fever and Sepsis

The interest in the constitutional symptoms resulting from bronchogenic carcinoma arises in part from the realization that their recognition may

contribute to an early diagnosis. Fever may result from ulceration and necrosis of the tumor itself or from the secondary obstructive and pressure effects of the tumor. The tumor may replace an entire lobe and form a large abscess after it has undergone necrosis. The fever may or may not be acute in onset and may be present either intermittently or continuously. A high fever is frequently the result of an extensive pneumonia or a lung abscess. Patients with lung cancer will frequently have some degree of chills and fever, at least intermittently. Night sweats occur, but not as frequently as in patients with tuberculosis Complicating evidence of inflammation may appear, e g. leukocytosis, increased sedimentation rate, anemia and tachycardia.

Loss of Strength

Weakness, loss of weight, anorexia, cachexia and fatigue are characteristic findings in advanced stages of bronchogenic carcinoma. At times, however, they occur early in the course of the disease and are initial symptoms in 2 to 3 per cent of cases In most instances they result from secondary suppurative processes, but they may occur when the infection is mild, when metastases are absent and when the tumor is small. The loss of weight is frequently accompanied by lassitude out of all proportion to objective findings These symptoms, when accompanied by cough or other respiratory symptoms or signs, suggest the presence of a bronchogenic carcinoma.

Symptoms from Metastases

The initial clinical manifestations of disease may result from metastases. In such cases the patients first seek medical attention because of symptoms that are often atypical and bizarre Taylor and Waterhouse, in a review of 1,592 cases, found that the illness began with symptoms due to metastases in 11 4 per cent of instances. Neurologic symptoms were present in 6 1 per cent, superior venal obstruction in 2 3 per cent, voice changes in 1.8 per cent, dysphagia in 0 7 per cent and superficial metastases in 0 5 per cent of cases. This means that the disease may go through a long subclinical or latent stage, during which it is progressing despite the absence of manifestations. The manifestations of metastases, both as early and as late symptoms, are as variable as the parts of the body involved. Pain is the commonest early symptom Involvement of mediastinal structures and enlargement of mediastinal glands may lead to retrosternal pain, dyspnea, hoarseness, aphonia dysphagia or regurgitation. The hoarseness and aphonia result from involvement of the recurrent laryngeal nerve, the left being affected more commonly than the right because of its anatomic location The right recurrent laryngeal nerve may be involved at the base of the neck. Dysphagia is produced by infiltration or compression of the esophagus by tumor

masses Pleural metastases may occur early or late in the disease and produce pain and dyspnea. Hiccough may result either from pressure on the phrenic nerve or from a brain metastasis A clinical picture resembling coronary artery disease may follow invasion of the brachial plexus, with the patient complaining of pain in the chest and shoulder which radiates down the upper extremity Metastases in the central and peripheral nervous systems may produce such diverse manifestations as headaches, dizziness, aphasia, hemiparesis, blindness, convulsions and coma At times, patients have been operated on for brain tumors that were found to be metastatic lesions Galuzzi and Payne, in a study of 647 necropsies, found that the brain was involved in 26 per cent of cases. Osseous metastases, the vertebrae being a common site, often cause severe localized or referred pain and are responsible for pathologic fractures Involvement of the abdominal organs and lymph nodes may cause epigastric pain, dysphagia, jaundice and vomiting, and produce a picture similar to that caused by a pancreatic or biliary tract malignancy. Jaundice as an initial symptom has been reported. Foster reported migrating phlebothrombosis as an initial symptom and reviewed the literature on this subject

Just as debility in a patient does not indicate an inoperable tumor, so physical vigor does not prove the reverse. Of patients seeking medical attention for symptoms arising from metastases, many appear to be in excellent physical condition Such patients, however, usually fail rapidly after the onset of symptoms

Physical Examination

The patient is apt to seek medical attention because of one or more complaints which may be mild in nature and nonspecific in type In most instances, he will have at least one respiratory complaint Although it is impracticable to hospitalize all such patients for diagnosis, a physical examination is obligatory In many instances of lung cancer abnormalities such as a localized wheeze, diminished breath sounds or a change in transmission of voice sounds will be found The physical findings are caused by the tumor or its metastases or by infection secondary to the tumor Cases have been reported in which abnormal physical findings preceded roentgenographic changes The physical findings will vary with the size, location, growth characteristics and sequelae of the tumor, especially the degree of bronchial obstruction and infection These sequelae include emphysema, atelectasis, pneumonitis and lung abscess, and the physical findings are characteristic for each.

The absence of physical findings in symptomatic or asymptomatic patients does not exclude the diagnosis, since the examination may show no abnormal findings at a time when there are roentgenographic changes. The

presence of physical findings may only delay the diagnosis, since bronchogenic carcinoma can simulate many diseases The chief value of abnormal physical findings in the chest is that they make it mandatory for the physician to request further studies, the most important of which is a chest roentgenogram The physical examination can frequently determine whether the lesion is operable and what the prognosis may be.

Wheeze

A unilateral and localized wheeze or rhonchus in a patient over the age of 40 is almost pathognomonic of bronchial obstruction. It is often inconstant and may be heard in one position but not in another. The wheeze may or may not be associated with dyspnea, depending on the site of the bronchus involved A bilateral wheeze suggests the possibility of tracheal obstruction. A wheeze due to a tumor cannot be distinguished from sounds produced in normal bronchi by loose mucus, although it tends to be localized, is more dry and brassy in character and does not disappear with cough. It is sometimes helpful if the patient is given one-half to one grain of codeine an hour before arising and is then examined immediately on arising. The codeine suppresses the cough reflex, resulting in accumulation of sputum at the point of obstruction. When the patient is examined, the wheeze usually is prominent and readily localized

Wheezing is a manifestation of the ball valve action of the intrabronchial tumor It is transient in nature, disappearing when obstruction is complete. For this reason, perhaps, it is rarely reported as an initial symptom of bronchogenic carcinoma and occurs at some phase of disease in only 10 to 15 per cent of cases Unfortunately, when it does occur the wheeze is often considered insignificant by the patient or may not even be noticed It may be regarded by the physician as a manifestation of bronchial asthma or congestive heart failure. Patients sometimes report that a period of wheezing preceded episodes of acute "pneumonia."

Emphysema

The wheezing stage is frequently followed by some degree of emphysema. The amount of emphysema depends primarily on the location of the tumor and the degree of bronchial obstruction it has produced. During inspiration, air passes into the distal bronchi, but on expiration it is often trapped, producing regions of focal emphysema. Because bronchogenic carcinoma is characteristically located in the primary and secondary divisions of the bronchial tree, the emphysema may be extensive and associated with dyspnea. It may be detected by diminished motion on the affected side, hyperresonance on percussion and diminished or absent breath sounds on auscultation. Emphysema is suggested by unilaterally diminished respiratory

movements The clinical signs are ephemeral, disappearing as the bronchial occlusion becomes more complete. The air is then absorbed, and the emphysematous regions are converted into atelectatic ones.

Atelectasis

Atelectasis follows complete occlusion of a bronchus by tumor and secretions and is usually associated with varying degrees of dyspnea The secretions and the atelectasis may clear following coughing and treatment by postural drainage and bronchodilators With progressive disease leading to massive atelectasis, the trachea and cardiac impulse are deviated to the involved side, the intercostal spaces become narrowed, the diaphragm becomes elevated and the affected hemithorax is retracted There is impaired fremitus on palpation, the percussion note is dull or flat and the breath sounds are diminished or absent over the atelectatic regions

Pleural Effusion

A pleural effusion may result from lymphatic blockage, a pulmonary infection or a peripheral pulmonary infarction (Ballantyne et al.), and is not necessarily the result of tumor spread to the pleura Peripheral tumors are more likely to involve the pleura earlier than central tumors Rapid formation of fluid may cause sudden occurrence of dyspnea The pleural *fluid resulting from metastatic spread is hemorrhagic in about 30 to 50 per* cent of instances, and tends to reform rapidly following thoracentesis Chylous effusions have been reported on rare occasions. Pleural effusions occur at some time in the course of the disease in 20 to 30 per cent of cases but are the initial symptom in less than 1 per cent The physical findings are those found in any pleural effusion, namely, dullness to percussion, decreased or absent breath sound and displacement of the heart to the opposite side. The physical findings of a small effusion may appear before roentgenographic changes occur. Any pleural effusion in the patient over age 40, especially when hemorrhagic, is likely to be carcinomatous in origin Other causes, however, such as tuberculosis, pulmonary infarction and congestive heart failure must not be excluded.

Hypertrophic Pulmonary Osteoarthropathy

Clubbing of the fingers and toes is not specific for bronchogenic carcinoma, but when present, can be helpful in establishing the diagnosis If the osteoarthropathy is accompanied by arthralgia it is more likely the result of bronchogenic carcinoma than suppurative pulmonary lesions or tuberculosis. The incidence as noted in different reports has varied from 5 to 10 per cent (Ray and Fisher; Wierman) Clubbing is one of the few extrathoracic signs which does not arise from a metastasis, although its specific

cause is not known The finding may accompany any chronic lung infection, but usually develops as a late complication. In contrast, in cases of lung cancer the symptoms may develop within a few weeks, may disappear rapidly after resection of the tumor and may return with recurrence of the growth. Flavell has reported reversal of the manifestations following vagotomy. No direct correlation exists between the size of the tumor, the degree of pulmonary infection and the osteoarthropathy, although the osteoarthropathy tends to occur more commonly with slower growing tumors, where infection, such as abscess and bronchiectasis, persists. Although clubbing usually appears relatively late in the course of the disease, it may be one of the initial complaints (Hansen). Bronchogenic carcinoma must be suspected whenever clubbing is found without an obvious cause. At times, the presence of arthralgia with pain and swelling of the hands, wrists, feet and ankles has led to a diagnosis of rheumatoid arthritis in cases which months later were diagnosed as bronchogenic carcinoma

Signs from Metastases

A search for metastatic lesions may seem somewhat academic during the preliminary physical examination Yet, such a search can be valuable in determining whether the disease is in an operable stage, since extrapulmonary metastases are contraindications for curative surgical procedures The tumor may metastasize by direct extension, implantation or via lymphatics and blood vessels. It may metastasize either early or late, and to all regions of the body The sites affected in five reported series are listed in table 3.

TABLE 3—*Sites of Metastases in Necropsy Material*

Organ	Ochsner and Debakey (1942) (1 047 cases) %	Farber and Tobias (1947) (200 cases) %	Bryson and Spencer (1951) (866 cases) %	Engelman and McNamara (1954) (234 cases) %	Caluzzi and Payne (1955) (741 cases) %	Senoo (1955) (336 cases) %
Liver	33 3	37 5	35 4	38 5	39 3	39 6
Adrenal	20 3	30 5	23 8	38	33 5	28 3
Brain	16 5	17 5	17	8 1	25.7	20 5
Bone	21 3	25	13	17.5	14 6	27 1
Pleura	29 8	25	—	11 1	—	31 3
Other Lung	23 3	21	—	14 6	—	28 9
Heart-Pericardium	12 3	11 5	9 3	11 1	—	27 1
Kidney	17 5	18 5	12 4	28 2	15 4	27 7
Pancreas	7 3	6 5	8 4	7 3	11.6	9 5
Spleen	3 5	5	4 0	5.6	5.3	7.4
Thyroid	2 3	3 5	2 2	0 9	3 6	5 1
Skin	3 6	5 5	3.6	3 4	—	1 5
Nodes-Cervical	17 4	15	8 9	18	—	17 7
Bronchial	69 7	63 5	—	53 9	—	98 7
Abdominal	20 7	12	13 8	18	—	—
None	—	14	27 7	—	—	0 8

Many of the metastases are not recognizable clinically. Senoo, in a careful study of necropsy material, found metastases in 99.1 per cent of 336 cases The thorax is mainly involved by direct spread, with distant metastases resulting from lymphatic and blood stream dissemination The tumor or its metastases may encroach on adjacent regions of the mediastinum, leading to pressure on the superior vena cava, esophagus, phrenic and recurrent laryngeal nerves Compression of the superior vena cava may produce distention of the superficial veins, as well as edema of the face, neck and chest Cyanosis may appear in these regions. Roswit and co-workers described the findings in 38 cases of the superior vena caval obstruction syndrome resulting from bronchogenic carcinoma This represented an incidence of 15 per cent in their series and is similar to the incidence of 14 6 per cent of superior vena caval obstruction syndromes reported by Szur and Bromley in 732 patients. Phrenic nerve involvement may lead to paralysis, progressive elevation and paradoxic motion of the hemidiaphragm. Vocal cord paralysis, the result of pressure on the recurrent laryngeal nerve, may be observed with a laryngeal mirror. Spontaneous pneumothorax has been reported as the initial feature (Heimlich and Rubin) This may follow invasion and necrosis of the pleura by tumor or it may result from rupture of a subpleural bleb in a region of obstructive emphysema If tenderness is elicited by deep pressure over a rib, rib metastases should be suspected If the tumor extends through the chest wall, it will be felt as a hard mass, which may undergo necrosis and ulceration. Enlarged and tender axillary, supraclavicular and cervical lymph nodes may be found. These nodes may also produce subcutaneous masses that can undergo necrosis and form draining sinuses Cardiac involvement may occur by direct extension or metastases, with tachycardia, arrhythmias, pericardial effusion, constrictive pericarditis and congestive heart failure as sequelae Right heart failure and cor pulmonale may result from generalized lymphangitic spread through the lung.

Abdominal masses, either superficial or deep, may be the initial sign of a metastatic focus Peripancreatic lymphadenopathy is indicated by hard nodular lesions in the epigastric region The common bile duct may be obstructed, leading to the typical picture of extrahepatic obstructive jaundice Metastatic hepatic lesions produce a large nodular organ, but rarely cause jaundice Splenomegaly may occur, but is usually not the result of metastases These intra-abdominal lesions often lead to recurrent massive ascites which may be hemorrhagic in nature. Although the kidneys and adrenal glands are frequently involved, these organs rarely can be palpated The adrenal glands are involved in many instances, although Addison's disease is a rare complication. A rectal examination may reveal peritoneal implantations which have collected in the rectovesical pouch

Metastases to the central and peripheral nervous system giving rise to symptoms or signs occur in 15 per cent of instances (Bryson and Spencer). Neurologic examination may reveal cranial nerve palsies, miosis, unilateral weakness or atrophy, peripheral neuropathy, abnormal reflexes and myopathy A clinical and pathologic study of the carcinomatous neuropathy and myopathy was made by Henson and co-workers. A picture typical of cerebral vascular occlusion may follow hemorrhage into or about a cerebral metastasis Some of the neurologic lesions may have resulted from other diseases or defects and may have preceded the carcinoma. The past history and results of previous examinations may substantiate this and turn what appears to be an inoperable tumor into an operable one

The ribs, vertebra, skull and long bones must be carefully palpated and percussed for regions of tenderness A metastatic focus to a bone may be located before there is roentgenographic evidence of abnormalities. This finding is often verified at necropsy when extensive bony metastases are found although recent roentgenographic studies had shown no abnormalities.

The Apical Tumor

The bronchogenic carcinoma of any cellular type located in the apical portion of the lung often gives a typical picture after it has spread locally For this reason, it was thought to be unique and became known as the Pancoast syndrome, or the "superior pulmonary sulcus tumor." Although bronchogenic carcinomas are the commonest cause of this syndrome, other benign and malignant primary and secondary tumors in this region, as well as noncancerous disease, may at times produce a similar picture (Chardack and MacCallum) The tumor tends to erode the bony cage because of the narrow region to which it is confined. It may destroy the upper ribs or infiltrate and exert pressure on the brachial plexus, the axillary vessels, the cervical sympathetic ganglia and the upper dorsal vertebra This results in pain about the affected shoulder girdle which may radiate down the arm to the fingers Atrophy, as well as weakness of the involved upper extremity, may follow Paresthesias are common symptoms Obstruction of the vessels may produce unilateral swelling of the shoulder and upper extremity. Involvement of the cervical and upper thoracic sympathetic nerves will result in Horner's syndrome, consisting of miosis, narrowed palpebral fissure, enophthalmos, as well as decreased sweating on the affected side Most of the initial symptoms and signs of the apical tumor are indications of extrapulmonary extension, so the condition is rarely suspected while it is still operable Clubbing of the extremities has been noted in association with apical tumors, and in some cases has been reported before clinical or roentgenographic evidence of disease Herbert and Watson reported 17 cases of apical tumors and listed the manifestations in 134 recorded cases

Course

Bronchogenic carcinomas follow no typical course Few patients recall the initial phases of the disease unless the onset, as with hemoptysis, is sudden or dramatic. Most cases start with a cough or pain in the chest which does not respond to treatment and frequently does not interfere with daily living The onset may be characterized by repeated respiratory infections occurring at any time of the year Although most patients have initial symptoms referable to the lungs or chest, many will complain of pain or discomfort arising from metastases in distant portions of the body. Therefore, the physician may be faced with a wide variety of possible diagnoses in each case.

The disease is usually far advanced at the time the patient enters the hospital, for it is at this time that disability, usually caused by metastases or complications, has developed The disease has probably existed for a long time, even in those instances in which the clinical manifestations have been present for only a short interval. The asymptomatic or latent period is particularly common in cases of peripherally located lesions. The occurrence of a long latent period is also shown by the finding of well developed bronchogenic carcinomas at necropsy in asymptomatic patients who have died suddenly from trauma or disease

Untreated bronchogenic carcinoma usually leads to death, within one year of diagnosis, although occasional survivals for as long as five or more years have been reported Bigwall reported a series of 255 untreated cases in which one-half died within 9 months from the appearance of the first symptom, 39 per cent survived longer than a year and 14 per cent longer than two years The latent phase of the disease was demonstrated by Rigler in a retrospective study of roentgenograms in proved cases of lung cancer. About 50 per cent of cases showed x-ray evidence of abnormalities for over two years before symptoms arose Approximately 2 to 5 per cent of all patients with bronchogenic carcinoma can be expected to survive five or more years after the diagnosis is made. Out of every 100 cases of bronchogenic carcinoma about 25 to 30 are operable, and of this group, resections are possible in 10 to 12 Of patients undergoing resection, only 2 to 5 will be alive five years later. The survival time is apparently not related to the sex or age of the patient, to the duration or severity of symptoms or the size *of the tumor (Rienhoff et al ; Watson). The survival period is often slightly* longer for patients with squamous cell carcinoma, which is relatively well differentiated, than for patients with an undifferentiated or an adenocarcinoma The most important factor for survival and a favorable prognosis is whether extrapulmonary extension has occurred Collier and co-workers in reviewing 100 cases of lung cancer in patients who survived over five years after surgical resection found that the presence or absence of blood vessel invasion, as seen microscopically, was closely related to survival The

over-all five year postsurgical survival in cases in which the diagnosis is made before extrapulmonary spread has occurred has been reported to be 30 to 40 per cent (Gibbon et al). It is this finding which makes early diagnosis so important.

Many causes account for the death of patients with bronchogenic carcinoma, *since death results more often from complications and sequelae* rather than from the carcinoma itself Most patients die of pulmonary failure and fibrosis secondary to the episodes of pneumonia, atelectasis, lung abscess and bronchiectasis that has often been associated with pleural effusion, pulmonary edema and congestive heart failure. On occasion, a massive pulmonary hemorrhage, cardiac involvement with arrhythmias, pericardial effusion or metastasis to a vital structure may kill the patient. Relatively uncommon causes of death are hepatic failure, cerebral vascular thrombosis, coronary artery occlusion and hemoptysis

SUMMARY

The relatively simple and preliminary procedures of the history and physical examination are the crux of early case-finding procedures in symptomatic patients Even though a diagnosis is generally impossible on the basis of such findings, the evidence, when carefully analyzed, may suggest a pulmonary lesion requiring further diagnostic studies On the basis of his initial findings, the physician must make the first important decision; he must decide whether additional studies are required The tragic error lies in not suspecting the disease at a time when surgical procedures may offer the only hope of cure

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CHAPTER 6

Diagnosis of Bronchogenic Carcinoma—Cytologic

By SEYMOUR M. FARBER, M.D., AND WILLIAM MANDEL, M D.

MOST PRIMARY CARCINOMAS OF THE LUNG are bronchogenic in origin and tend to exfoliate cells into the bronchial lumen. The normal current of secretions in the bronchi then carries tumor cells into the sputum where they may be detected by cytologic examination The cytologic method has advantages over other means for obtaining morphologic evidence of lung cancer because of its simplicity and because of the ease of obtaining repeated specimens for examination

DEVELOPMENT OF PULMONARY CYTOLOGY

In 1917, Stockard and Papanicolaou reported a method for the rapid fixation and staining of vaginal smears Using this method, Papanicolaou described cells which he could identify as malignant and reported such findings in 1933 This stimulated further work on the cytologic technic as a diagnostic procedure, ultimately leading to its clinical application for detecting cancer of the lung

A study of sputum from 250 patients with various types of pulmonary disease was reported by Wandall in 1944 He found neoplastic cells in the sputum in 84 of 100 proved cases of cancer of the lung In 1946, Papanicolaou demonstrated malignant cells in the sputum in 18 of 21 cases with proved cancer of the lung In the same year, Herbut and Clerf reported the diagnosis of 47 of 57 cases of lung cancer by the cytologic examination of secretions obtained by bronchoscopy In 1947, Woolner and McDonald analyzed 200 cases in which a diagnosis of carcinoma was made by cytologic examination of sputum and bronchial secretions

Our interest and initial experience in pulmonary cytology began in 1946. Since that time, more than 65,000 specimens of sputum, bronchial aspirations and pleural fluid have been examined cytologically in our laboratory The results have strengthened our confidence in the accuracy of the method for detecting malignancy Furthermore, the correlation of the results of cytologic examination of the sputum with other findings, by providing greater understanding of the natural history and course of lung cancer, may open up new avenues of therapeutic approach

Methodology

The successful application of exfoliative cytology for detecting lung cancer depends on competence in processing and examining the sputum. Considerable care must be taken in collecting the specimens and in preparing and staining the sputum for microscopic examination. The microscopic examination itself must be thorough, and the examiner must have adequate training and experience in pulmonary cytology.

Specimen Collection

Complete and detailed instructions to each patient on the proper collection of sputum samples is essential. Without the understanding and cooperation of the patient, nasal secretions or postnasal drainage which often cannot be distinguished from sputum by gross inspection, may be submitted for examination. In addition to verbal instructions, the distribution of printed instructions aids in obtaining proper specimens. The form we use reads as follows

Instructions for Sputum Collection

1 *Before breakfast on the morning the specimen is to be collected, clear your throat* and discard this material It is important to rinse your mouth with water if you have placed anything in your mouth—such as food, milk, coffee, mouthwash, toothpaste, etc *Do not contaminate the specimen with tobacco, cigarette ash, Kleenex, etc*

2 Breathe deeply 8 to 10 times, then cough deeply Collect the material obtained in this way for half an hour A small amount of material will be sufficient *if it has been raised from deep in your chest* Do *not* submit a specimen unless you believe it has come from deep in your chest

A covered glass or cardboard container is provided for collecting the specimen

Smear Preparation

Although smears should be prepared as soon as possible after collecting the sputum, a delay of four or five hours does not distort cellular detail, provided sufficient saliva or mucus is present to prevent drying. As an aid in selecting suitable material for smearing, the specimen is poured into a watch glass and examined over a dark background Three smears are prepared from differing types of material selected from each of 5 daily specimens, bloody flecks and cheesy particles, when present, should always be chosen The specimen may also contain small bits of tissue which can be smeared.

A small amount of the selected material is then placed on a clean glass slide with a pair of wooden applicator sticks and smeared to uniform thickness. Each smear is immediately placed in ether alcohol fixative where it

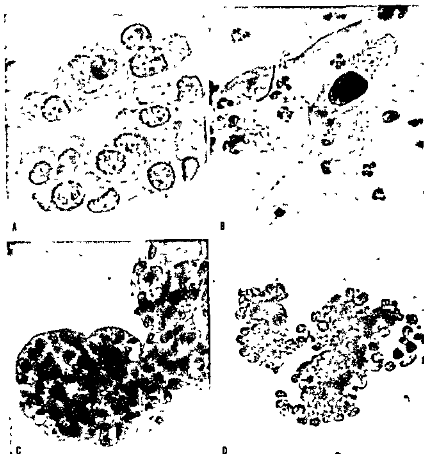


Fig 1—Photomicrographs of cells from sputum smears (A) Normal bronchial columnar epithelial cells (B) Malignant squamous cell, "tadpole" form (C) Malignant acinus from adenocarcinoma (D) Small, undifferentiated or "oat" cells

Staining

The Papanicolaou method of staining is employed in most laboratories. The procedure has undergone few modifications since its original description, although many workers have made minor alterations to conform to their own preferences

Microscopic Examination

It is important to thoroughly examine every area of an adequate number of slides Screening under low power magnification (× 120) is adequate, higher magnification (× 450), however, should be used to examine any suspicious cells A "hit and miss" examination or an "over-all" im-

pression does not suffice. The systematic screening of the slide by a competent trained cytotechnician is essential. Smears containing atypical cells are referred to a pathologist, specially trained in exfoliative cytology, for final diagnosis.

Normal and Nonmalignant Cells

Normal cells, defined as those seen in noncancerous conditions, may be classified as follows:

a *Squamous epithelial cells*—from oral mucosa, pharynx and larynx (from saliva). Basal or pavement cells, precornified or intermediate cells and cornified or superficial cells
b *Columnar epithelial cells*—from trachea and bronchial tree Tall ciliated and ciliated cuboidal cells (fig 1A).
c *Reticuloendothelial cells*—respiratory phagocytes Monocytes, histiocytes, macrophages and foreign body giant cells
d Blood and miscellaneous elements Leukocytes, lymphocytes, eosinophils, plasma cells, red blood cells, bacteria, fungi, yeasts, Curschmann's spirals, crystals and diatomes

General Criteria for Malignancy

The following can be used as a guide to the general morphology of exfoliated malignant cells

a Aggregate of cells Variation in size, shape and density of nuclei within the group, "crowding," molding, discrepancy of maturation of cells within a joined group
b Individual Cells 1 Cell—Large to giant in size, disproportion in ratio of nucleus to cytoplasm, bizarre shapes and unequal maturation of cytoplasm. 2 Nucleus—Enlarged, irregular, jagged contour, often with sharp protusions, aberrations of chromatin pattern. 3 Nucleolus—Enlarged, multiple, varied in size and shape, irregular in contour

Identification of Types of Tumor Cell

The aim of exfoliative cytologic studies is the accurate detection of malignant disease. *Identification of the specific type of lung cancer by cytologic* means is, however, not always possible. Nevertheless, differentiated types of tumor cells may often be identified by their distinctive cellular features (Spjut et al.; Umiker). Most authors distinguish at least three main types of pulmonary carcinoma, squamous, adenocarcinoma and anaplastic or undifferentiated carcinoma Cytologically, the cells from each of these forms may have similar nuclear features; the differentiation is made on the basis of differences in *cytoplasmic structures and the intercellular re*lationships of groups of malignant cells (figs. 1B–D). Just as the individual *lung cancers may show* histologic changes from one area to the next, so pleomorphism may occur among exfoliated malignant cells.

Diagnosis in Nonmalignant hest Conditions

The cytologic examination of the s mainly restricted to pa-

nary disease. Reports of collection of sputum after nebulization of various solutions are encouraging (Allan et al ; Bickerman et al); however, they have not proved practical for patients who are unable to raise sputum

In nonmalignant lung disease the sputum may contain cells which show features resembling malignant cells Despite this, when the cytologic examination is done by experienced personnel, the false diagnosis of malignancy is rare (Farber; Umiker) Some conditions which yield bizarre cells are squamous metaplasia of bronchial epithelium, pulmonary infarction, bronchiectasis, bronchial asthma and lung abscess (Farber, Rosenthal et al , Umiker) The microscopic examination of stained sputum may disclose findings which may be helpful in diagnosing nonmalignant chest conditions (Farber; Wood, et al).

Discussion

The results of the cytologic examination of specimens in our laboratory demonstrates the usefulness of the method

	Group I	Group II	Combined
Number of Specimens	6,281	5,501	11,782
Number of Patients	2,066	1,832	3,898
Proved Lung Cancers	241	206	447
Over-all Accuracy of Cytologic Method	55%	60%	58%
Accuracy with Bronchial Aspirates Alone	33%	39%	37%
Accuracy when 5 Specimens Submitted	90%	87%	89%

The incidence of carcinoma of the lung was approximately 11 per cent The cytologic technic was sufficiently sensitive to detect only slightly more than one-half of the malignancies, this relatively low number may be attributed to the fact that an average of only 3 specimens were received for examination When 5 separate sputum specimens were examined, a cytologic report of malignancy was made in 89 per cent of instances Approximately 40 per cent of cases of lung cancer can be detected by cytologic examination of a single sputum specimen, this is increased to about 60 per cent when 3 daily specimens are examined and to 90 per cent when 5 specimens are examined If malignant cells do not appear in the first five speciments submitted, they are unlikely to appear at a later date

There has been some controversy concerning the value of bronchoscopically obtained secretion versus the use of sputum for cytologic examination (Rome and Olsen) Some have belittled the value of sputum specimens, asserting that the malignant cells are obscured and diluted by respiratory tract secretions Bronchial secretions, they contend, may be taken directly from suspicious areas and thus are more suited for cytologic examination Dilution by bronchial tree secretions has little, if any, effect on the use of sputum for cytologic examination (Farber and Pharr) Both bronchial secretions and sputum may contain bizarre cells Sputum is more easily

obtained than bronchial aspirates and its use for cytologic examination permits repeated studies on each patient, as well as the study of more patients. We have often found that the sputum raised immediately after a bronchoscopic examination contains more diagnostic material than that obtained by direct aspiration. The greatest accuracy we have achieved (92 per cent) resulted from cytologic examination of both bronchial aspirates and 5 daily sputum specimens.

Because no single cell characteristic is by itself pathognomic of malignancy, a positive diagnosis depends on an evaluation of several microscopic findings. The diagnosis of malignancy based on cytologic examination is not less reliable than the diagnosis based on tissue specimens; it is only that the criteria are somewhat different.

A difficulty of the cytologic method for detecting lung cancer is that it is not feasible to eliminate the possibility of the chance shedding of cells. Every malignant tissue presumably exfoliates cells into adjacent cavities and tissues. Since bronchogenic carcinomas originate in the basal layer of cells in the bronchi, some cancer cells will enter the bronchial secretions Theoretically then, almost all bronchogenic carcinomas should be diagnosed by the cytologic examination of sputum or bronchial aspirates. There are, however, clinical limitations in making the diagnosis by this method. In the first place, when the tumor occludes the bronchus, the adjacent inflammation may seal it from access to the tracheobronchial tree In addition, although countless numbers of cells are exfoliated, not every sputum collection will contain such cells The intermittent finding of malignant cells in the sputum of patients with lung cancer is not unusual For this reason, and because of the unavoidable chance selection of material for smearing, the optimum use of the cytologic method depends on examination of an adequate number of specimens

The cytologic diagnosis of lung cancer may be particularly effective when the malignant lesion is in its early stages of development, for the younger and smaller tumors may often exfoliate more cells into the secretions than older and larger tumors.

The technic of cytologic examination requires further evaluation and modification. It is without question a major advance in the diagnosis of lung cancer, but its maximum effectiveness has not yet been achieved. The first need was to establish its reliability which, in general, has been already accomplished.

The accuracy of cytologic examination of the sputum is such that Woolner and McDonald advised exploratory operations on the basis of positive cytologic findings. The greatest value of cytology might be in the periodic examination of males past the age of 40. Although this is time-consuming and expensive, the fact tha cytologic diagnosis may give evidence of bron-

chogenic carcinoma before roentgenologic changes suggest that it may be an important case-finding method In any event, it can be the most valuable single diagnostic procedure for investigating minimal pulmonary symptoms when physical findings or roentgenographic changes are lacking

Summary

The value of the cytologic method for detecting lung cancer is now established When an adequate number of sputum specimens are examined by well trained personnel, the accuracy of the method in detecting the presence of lung cancer approaches 90 per cent The erroneous diagnosis of malignancy is low Widespread use of the cytologic technic in persons in the age groups most susceptible to lung cancer and in those with minimal pulmonary symptoms can be expected in increase the numbers of diagnoses which can be made at an earlier date

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CHAPTER 7

Roentgen Diagnosis of Bronchogenic Carcinoma

By LEO G RIGLER, M D.

THE ROENTGEN FINDINGS IN CARCINOMA OF THE LUNG should be considered in two categories Roentgen examination may serve as a means of detecting the condition, frequently in a presymptomatic stage Under these conditions of detection, certain signs appear and are of great importance The roentgen examination may also be a means for the differential diagnosis and identification of a lesion which is symptomatic and presents x-ray signs and other evidences of an abnormal process

DETECTION OF CARCINOMA OF THE LUNG

It is perfectly clear from studies during the course of mass surveys, hospital admissions and especially thru the retrospective study of patients known to have carcinoma of the lung, that x-ray findings may well be present long before the onset of recognizable symptoms In our own series, we considered that there were clear evidences of an abnormality in the lung, in an area in which carcinoma later was proved to be present (fig 1), on an average of 9 months before the onset of symptoms which were directly related to the carcinoma That there are rare cases in which symptoms and even bronchoscopic findings occur without the presence of positive roentgen findings is perfectly clear Likewise, cases have been reported in which definite carcinoma cells have been found in the sputum, and yet the roentgen examination appeared to be entirely normal In some of these cases, the statement is questionable, since on close examination, there actually have been evidences of pulmonary findings In our own experience, in some 400 cases, there were only three in which patients had symptoms without demonstrable roentgen findings This may have been an unusual series, but I am confident that this is an uncommon, if not a rare, occurrence

In the detection of a lesion, it is apparent at once that some consideration must be given to the technic of examination A single posteroanterior view of the chest or a minifilm of similar character, while it will serve to detect the vast majority of lesions, may well be insufficient to encompass all the



Fig 1—Development of a nodule in the lung over a 6 year period One year after the last roentgenogram, symptoms developed and a pneumonectomy revealed adenocarcinoma. While the time elapsed in this case is unusual, *it is not uncommon to find roentgen signs of* a lesion of this kind, several years before there are any symptoms (From RIGLER, L G · X-ray diagnosis of cancer of the lung Postgrad Med *18* 361–373 [Nov] 1955

smaller changes which bronchogenic carcinoma produces. A distinct increase in the number of cases which are readily detectable occurs when two films are made These may be stereoscopic posteroanterior views or one anteroposterior and one posteroanterior view. An additional lateral view will also add to the probability of detection but only a few more cases would be found in this way. The addition of oblique views, of films made in the position of lordosis, in inspiration and expiration, and of a film made with high kilovoltage or marked overexposure with a grid, would add another small increment to the number of cases which could thus be detected.

For the intensive study of any patient who has symptoms, I would suggest the following procedure Stereoscopic posteroanterior and one lateral film should first be made in order to detect an abnormal shadow. If there is no abnormal finding, films should be made in *expiration* as well as in inspiration, in order to determine the possibility of obstructive emphysema In the presence of symptoms or other evidences suggestive of carcinoma, where there are no abnormal shadows seen in the conventional film, body section roentgenograms of both lungs should be made In such films, small nodules in the lungs or masses in the mediastinum, not visible with the usual procedures, will occasionally be revealed In addition, various oblique views may be helpful.

If a lesion is found, regardless of whether the lesion is peripheral or central, body section roentgenograms are also of the first importance In the former case, the delineation of the exact nature of the shadow in the lung is far better accomplished by this means. The presence or absence of calcium, of additional lesions and the character of the surrounding lung can thus be determined. If the abnormality appears to be central, the

planigrams may serve to demonstrate the lumen of the bronchi and thus the nature of the process. Finally, in those cases in which there is strong evidence of a lesion, bronchography with contrast medium may be a final determining factor and serve to localize the process as well.

The roentgen findings of bronchogenic carcinoma are exceedingly variable, for this lesion is the great simulator of all other types of disease of the lungs A pathologic state which may produce a growing mass in the lung, necrosis and abscess formation, secondary inflammatory reaction, perilymphatic and perivascular infiltration, partial or complete bronchial obstructions, segmental or otherwise, with all the pulmonary sequelae which follow such obstruction, obviously may give a great variety of roentgen findings

In the early stages of the disease, particularly in the presymptomatic period, the roentgen findings may be some what as follows

1 A solitary mass in the lung field usually a spheroidal nodule The shadow seen represents the growing tumor It may be small enough and so peripheral that it produces no symptoms, but roentgenographic findings may be highly suggestive of carcinoma (fig 1)

2 Cavitation, resembling a solitary abscess (fig 2) Often there are distinctive signs of tumor which will be considered later

3 An area of consolidation (fig 3) It may resolve in part but usually leaves a residue Almost always such lesions are accompanied by symptoms

4 An infiltrating shadow, extending up along the vessels in linear fashion resembling tuberculosis (fig 4)



Fig 2—Solitary abscess in the lung resulting from squamous cell carcinoma (A) Irregular infiltration of the lung as seen in the conventional roentgenogram. (B) Planigram reveals a cavity with a very thick wall The excrescences around it represent extensions of the tumor The appearance is typical of carcinomatous abscess (From Rigler, L G, and Heitzman, E R Planigraphy in the differential diagnosis of the pulmonary nodule with particular reference to the notch sign of malignancy Radiology 65 692–702 [Nov] 1955)



Fig 3—Postero-anterior roentgenogram and planigrams in a patient with symptoms of pneumonia The dense shadow in the right upper lobe resembling lobar pneumonia actually is the result of atelectasis from a carcinoma of the right upper lobe bronchus. The bulging inferior margin is suggestive of the tumorous nature of the process There is, no doubt, a large element of pneumonitis as well In the lateral planigram, the obstruction of the anterior branch of the right upper lobe bronchus is exhibited (arrow). In the postero-anterior planigram, the abrupt ending of the air column in the same bronchus is shown The presence of such obstructions in association with a pneumonic lesion is characteristic of carcinoma (From Rigler, L G The roentgen signs of carcinoma of the lung Am J Roentgenol 74 415–428 [Sept] 1955)



Fig 4—Infiltrating carcinoma of the left upper lobe The diffuse shadow extending from [illegible] tuberculosis [illegible] al branch of [illegible] diagnosis of [illegible] lung Am J. [illegible] carcinoma (From [illegible] Roentgenol 74 415–428 [Sept] 1955)



Fig 5—Pulmonary sulcus tumor, right apex The first film shows only an infiltration into the apex, a small, solid mass in the medial portion of it, and definite involvement of the pleura The second film made 4 months later shows a marked erosion of the third and fourth ribs, in addition to a considerable increase in the infiltration of the lung The findings are fairly characteristic of apical carcinoma, often called the Pancoast Tumor (From Rigler, L. G A roentgen study of the evolution of carcinoma of the lung J Thoracic Surg 34 283-297 [Sept] 1957)

5 In rare cases a small apical shadow of solid character, appearing to arise from the superior surface of the lung Erosion of the surrounding bony cage will appear later (fig 5)

6 An enlarged hilum

This is probably one of the commonest and most overlooked of all the early signs It is usually unilateral Increased density of the hilum together with some obliteration of the normal aerated space between the hilum and the mediastinum is an important sign Mensuration of the hila may be helpful in establishing a distinct difference in size between the two sides, thus suggesting an abnormal mass Absence of measurable differences in size certainly does not exclude a tumor

7 Segmental or lobar emphysema

8 Segmental or lobar atelectasis

It is uncommon to find evidences of bronchial obstruction without symptoms, but occasionally segmental areas of emphysema or atelectasis may be seen without any appreciable illness In rare cases, emphysema may be found in the presymptomatic stage.

Differential Diagnosis

As stated above, the problem of differential diagnosis of carcinoma of the lung from many other pulmonary lesions is an extremely difficult one With the increasing use of roentgen examination in apparently normal individuals, the problem is even more pressing, since the finding of an abnormal shadow in the roentgenogram puts a grave responsibility on the physician in charge Likewise, the appearance of symptoms such as cough, pain in the chest, and hemoptysis, all of which may be produced by a

great variety of nontumorous lesions, makes differential diagnosis exceedingly important.

There are many methods whereby a *definitive diagnosis of carcinoma* of the lung may be established. The most cogent of these, of course, is microscopic examination of tissue removed either through the bronchoscope, by percutaneous biopsy, or as a result of thoracotomy. The demonstration of carcinomatous cells in the sputum or in bronchial aspirates is another effective method for the positive identification of lung cancer. Yet there are still a substantial number of patients either with an abnormal shadow in the roentgenogram or with symptoms, with whom none of these methods is effective. The procedures may either be unavailable, not feasible in the particular case, ineffective or give equivocal results. Despite the easy assurance of thoracic surgeons and the relatively innocuous character of exploratory thoracotomy, there are many cogent reasons why certain patients cannot be submitted to this procedure. Bronchoscopy, too, has many limitations This is, of course, particularly true of the peripheral spheroidal nodules which are now so commonly being found, for they are rarely reached by the bronchoscope The numerous limitations of examination of the sputum are well known and need not be reiterated here For these many reasons, the use of roentgen findings for the definitive diagnosis may be of great importance in specific cases

It is usually held that, while roentgen examination may be of great value as a means of detection, its utility as a method of identification is sharply limited. That there are distinct limitations in the roentgen determination of the exact nature of any disease process, no one can gainsay. But there are distinctive roentgen signs which seem so characteristic of malignant tumors that they carry with them very great weight, almost to the degree of the positive finding of carcinoma cells whether in the biopsy specimen or in the sputum. It should be emphasized that all diagnoses including those derived from autopsy findings are only probabilities Certainly, some errors occur in interpretation of the bronchoscopic biopsy, in the bronchoscopic observation of tumors, and even in biopsies obtained from exploratory thoracotomies. Obviously, the errors which are inherent in differential diagnosis by means of roentgen examination are much greater than those by microscopic examination. In many cases, however, this is the only method available and must be utilized The large number of solitary spheroidal shadows found in the lung on routine examination, the smaller number of minor pulmonary infiltrations which we are encountering in apparently normal individuals, and the numerous patients with chronic pulmonary disorders whose findings simulate those of carcinoma, demand the utmost consideration of the roentgen findings in differential diagnosis. Under such circumstances, the most intensive roentgenologic studies should

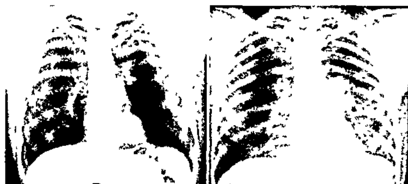


Fig 6—Carcinoma of left lower lobe bronchus An enlarged left hilum, with obstructive emphysema of the left lower lobe, is found on the first examination The second roentgenogram 2 years later shows a more marked enlargement of the left hilum The emphysema of the left lower lobe has now been converted into a beginning atelectasis because of the increasing obstruction of the bronchus (From Rigler, L G X-ray diagnosis of cancer of the lung Postgrad Med *18* 361–373 [Nov] 1955)

be undertaken, unless the diagnosis becomes established by other methods earlier

Of the first importance is the comparison of films made at various times in the history of the patient A very high percentage of our adult population at the present time will give a history of having had a roentgenographic examination of the chest, often fortuitously, at some previous date Whether done by the photofluorographic method or by the use of full sized films, such records should be preserved for many years This is especially true for the so-called "negative" roentgenograms, for often such films actually exhibit the evidences of a very early lesion, not sufficiently apparent to be detectable at the time, but easily seen in retrospect when a larger lesion is found later

None of the roentgen signs to be described below are absolutely diagnostic, but the positive findings have such a degree of reliability that they are sufficient to present a firm indication for exploratory thoracotomy at the very least It should be re-emphasized that all the clinical and laboratory findings must be considered in the differential diagnosis

Definitive Roentgen Signs of Carcinoma of the Lung

The appearance of a solitary pulmonary shadow not present in previous films, especially in an individual past middle age, is of very great significance It is obvious at once that here there must have been a previous examination at a period of time usually longer than three months before the one under consideration Frequently, such a situation is encountered in individuals who were relatively free of symptoms at the time of the first ex-



Fig 7—Carcinomatous nodule, left upper lobe (A) The nodular lesion is suggestive, but not necessarily diagnostic of carcinoma A film made a year earlier (B) shows no evidence whatever of this lesion at that site The combination of the two films makes the diagnosis of carcinoma highly probable (From Rigler, L G : The Detection of Cancer of the Lung Proceedings of the Third National Cancer Conference (June 4–6) Philadelphia J B Lippincott, 1957, pp 515–520)

amination The complete absence of any evidence of a lesion in an area which in later films shows infiltration or a nodule is a specific indication for resection of the area with more radical procedure if the diagnosis of carcinoma is confirmed microscopically at the time of operation (fig 7).

The demonstration, in an individual over 40, of a nodular pulmonary shadow which was not present in films made six months, a year or several years before, is not by any means complete assurance that the lesion is a tumor or that it is malignant. We have learned in recent years that granulomas will likewise appear suddenly in middle-aged individuals. But I believe this is, by far, the exception and not the rule. A lesion of this kind appearing suddenly is much more likely to be a carcinoma than it is to be a benign process or a granuloma.

The demonstration of a peripheral pulmonary mass or nodule in the lung which shows an increase in size when compared to a previous film is likewise of very great importance. This is perhaps an even more cogent indication of the presence of a malignancy than the sudden appearance of a shadow in an area in which none was previously seen. But, again, there are exceptions since granulomas and hamartomas may occasionally increase in size under observation. It should be noted, in this connection, that a failure to increase in size does not at all exclude carcinoma Some malignant tumors grow very slowly. I have observed cases of carcinoma which took as long as seven years to attain a considerable size Furthermore, I have observed at least one case in which over a period of four years there was no change whatever in size, although it proved to be an adenocarcinoma of the lung. De-

spite these rather startling exceptions, a lesion which has increased in size over a period of one year, especially if the increase is reasonably rapid, is most probably a carcinoma and should so be regarded until proved otherwise

In any solitary peripheral pulmonary nodule, the possibilities of diagnosis are always very difficult Some thirty conditions may produce such a shadow in the roentgenogram Planigraphic studies, however, may be of very great value in determining whether or not the lesion is malignant or benign. By this means, an accurate determination as to the sharpness of outline, the homogeneity, and the contour of the lesion can be obtained. None of these characteristics are highly diagnostic, however, since granulomas may be quite sharply rounded while tumors may or may not be sharply defined The homogeneity, likewise, is not distinctive since cavitation or necrosis may occur both with tumors and with inflammatory processes The contour may be of some importance because most tumors tend to be reasonably regular in their outline and to assume a spheroidal shape, whereas inflammatory lesions may be much more irregular and much less geometric in form. The tendency for inflammatory lesions and for infarcts to be segmental helps in differential diagnosis Benign tumors, however, may also be spheroidal

Of great importance is the demonstration of the presence or absence of calcium in the mass Such a determination is best made by planigraphy; the procedure is highly effective in demonstrating calcium. While it is true that the absence of calcium is of little significance, since may granulomas and benign lesions do not show calcium, the presence of calcium is of great significance A few cases, both of bronchial adenoma and of carcinoma, have been reported in which calcium was demonstrated within the lesion itself In some of these the calcium may well have been present prior to the development of the tumor which happened to occur in the same area In others, necrosis of the tumor resulted in calcification Nevertheless, these are exceptions to the general rule The character of the calcification may be of considerable importance Ringlike or laminated calcification almost never occurs with carcinoma Finely stippled areas may be seen in carcinoma but are far more common in hamartomas For practical purposes, however, the presence of calcification, barring compelling evidence to the contrary, should indicate that the lesion is not a malignant tumor

A solitary abscess, even rather small in size, may be the first indication of a carcinoma of the lung (fig 3) Such abscesses are usually the result of necrosis within a rapidly growing tumor The distinction from an ordinary pulmonary abscess or from a tuberculous cavity can very commonly be made, especially if laminagraphy is undertaken. Carcinomatous abscesses will usually show a protruding outer margin which extends well beyond the

area of the cavity itself. The appearance of this protrusion is characteristic of a growing mass. In my own experience it has been present almost invariably in the carcinomatous abscesses, especially if one obtains good planigraphic studies so that the clear delineation of the outline of the borders of the cavity could be made In the larger cavities the presence of masses within the air pocket itself can be made out, indicating tumor nodules growing within the cavity. It is sometimes difficult to distinguish such shadows from those produced by granulations but, as a matter of fact, it is uncommon for a nontuberculous abscess or a tuberculous abscess cavity to show such masses within the air space The demonstration of a cavity within a solitary nodular lesion without other pulmonary changes, especially if found in an individual over 40 years of age, is very strong evidence for carcinoma

In the course of our study of a great many nodules in the lung, we have come upon a sign which appears to be highly suggestive of malignancy. This consists of a notching or umbilication in the margin of the shadow (fig 8). The deformity is not well seen in the ordinary roentgenograms, although occasionally we have seen it here as well, but it is quite clearly delineated in body section roentgenograms when the film is made at the proper level The cause of this notching is not entirely clear although in several sections, which we have seen histologically, it appears to resemble a hilus in the mass, containing blood vessels and normal lung structures extending into the body of the mass itself, thus producing the irregularity of the contour. The notching is usually single although in some cases it has been multiple. I have observed this in pulmonary metastases, such as from hypernephroma or melanoma, as well as in primary malignancies Assuming that a solitary metastasis is an indication for extirpation, the presence of this notch seems to be a prime indication for immediate surgery with extirpation of the lesion In a few cases, the notch has been found in hamartomas and even in granulomas so it is not completely diagnostic It is important to be certain by use of multiple sections that the notch is really within the mass and not an overlapping shadow.

It should be noted that the absence of this notch does not by any means exclude malignancy. While we have found it in small as well as large lesions, it appears more obvious in the larger lesions *We have, however, seen it in* lesions as small as 1 cm in diameter. I would emphasize that the presence of such a notch, as seen in laminagraphic studies, is of utmost importance in determining that the patient should be explored and microscopic study undertaken.

A change in the size and appearance of one hilum is a lesion likewise of very great significance and only possible to observe when previous films are available (fig. 9). Increases in the size of the hilum occur in probably 50 per cent of all the carcinomas of the lung. They are difficult to interpret



Fig 8—Peripheral epidermoid carcinoma of the lung increasing in size with specific signs in the planigram (A) The first film, made in 1951, shows no evidence of a lesion (B) The second film, made in 1952, shows a small lesion in the right lower lobe (arrow) representing the first evidences of the carcinoma (C) The third examination in 1953 exhibits a great increase in size (arrow) (D) In the planigram, a cavity is seen within this hard solid mass On its inferior surface, there is a distinct umbilication or notch which is highly suggestive of the carcinomatous nature of the process (From Rigler, L G : X-ray diagnosis of cancer of the lung Postgrad Med 18 361–373 [Nov] 1955)

because of the common occurrence of irregularities in this region resulting from inflammatory changes and other disease processes in the lung. Nevertheless an enlargement of one hilum, even by itself, should be considered a carcinoma until proved otherwise If the hilum seems to have been enlarging while under observation, the probability that it is a carcinoma is extremely high much higher, in fact, than if one sees a peripheral lesion enlarging

Attempts at measurement of the hila have been made but have not been



Fig 9—Epidermoid carcinoma of left upper lobe bronchus exhibiting characteristic increase in size of hilum (A) The first film shows an enlarged left hilum (arrow). (B) The second film made 18 months later shows a moderate change with increasing infiltration around the hilum (arrow) (C) The third film, only 7 months later, shows a massive increase in the size of the hilum shadow which now has a lobulated appearance, characteristic of tumor mass (From RIGLER, L G X-ray diagnosis of cancer of the lung Postgrad Med *18* 361–373 [Nov] 1955)

satisfactory. This results from the difficulty of finding an end point on the lateral side and the necessity of fixing arbitrarily on the end point of the thorax on the medial side Nevertheless, in doubtful cases, a disproportion in the transverse diameter of the two hila of more than 1.7 cm., measuring from the midline to the outer border of the large vessels, is of great significance and should lead to more intensive investigation.

Another sign of great value is the tendency for carcinomatous enlargement of the hilum to obliterate the clear area between the major branches of the pulmonary artery and the mediastinum. This usually does not occur in other types of hilar enlargement.

It is at once apparent that the demonstration or even the suspicion of enlargement of the hilum should call for intensive roentgen study. Several positions including oblique and lateral views should be made Such films will often permit a more definite determination as to whether the shadow seen is truly in the hilum and not in the parenchyma of the lung superimposed upon it, and whether an actual enlargement is present. Under such circumstances also, roentgenograms made in inspiration and expiration may be of very great value. For a hilar enlargement of carcinomatous origin is usually the result of a tumor arising in one of the major bronchi which has extended into the peribronchial tissues. Such tumors very often produce sufficient obstruction of the bronchus to exhibit an obstructive emphysema in the area supplied by the involved bronchus It is best brought out in expiration; this is an extremely important maneuver in determining definitely whether an actual tumor is present.

Further steps should include planigraphy, in an effort to visualize the

major bronchi, since an enlargement of the hilum is almost always associated with a tumor arising in a bronchus of the first, second or third order. Furthermore, the presence of enlarged lymph nodes can be effectively determined in this fashion. If the planigraphic study is not entirely satisfactory, that is, if the major bronchi are not clearly visualized throughout, it may be necessary to go a step further and do bronchography with an opaque medium The latter should lead finally to a definitive determination as to whether or not any partial or complete obstruction of a bronchus is present and the nature of that obstruction.

An infiltrative lesion in the lung is perhaps the most difficult of all to differentiate, particularly from the various forms of pneumonitis and from tuberculosis There are two roentgen signs which are of some value in this differentiation. The first is, again, the demonstration over a period of time of the increasing character of the infiltrative process While it is true that this may occur in tuberculosis and other chronic lesions, usually it is much slower and less obvious, while in carcinoma the infiltrative process may gradually, but usually much more rapidly, increase in size and extent of involvement Secondly, in such infiltrative lesions, a nodular beaded character can be demonstrated which is highly significant (fig 10). I would say at once that the definitive character of such lesions is far from that which I have discussed under the peripheral lesions or the enlarged hilus Nevertheless, an infiltrative lesion which exhibits these nodulations along its course should certainly be considered highly suspicious, at least, of malignancy, despite its resemblance to an inflammatory process in other respects

The pneumonic lesions are among those which give us the greatest difficulty in differential diagnosis. There are three roentgenologic findings which should arouse suspicion (1) The failure of an ordinary pneumonia to resolve should be regarded as indicative of either carcinoma or a chronic process until proved otherwise The diagnosis of unresolved pneumonia undoubtedly is correct in some cases, but it is a highly risky diagnosis and should never be made without the most careful and repeated observation with roentgen examination (2) Planigraphic studies of such areas of infiltration of the lung, which are thought to be pneumonia, may again reveal a nodular type of mass rather than one with a linear or segmental distribution This should suggest its carcinomatous origin Furthermore, a typical bronchostenosis may be demonstrated in this way. (3) Bronchography should be undertaken if the bronchi are not clearly delineated in the planigram for very often in carcinomatous lesions, which imitate pneumonia or have associated pneumonitis, bronchostenosis can be demonstrated Bronchostenosis does not accompany pneumonitis, it seldom occurs with chronic tuberculosis of the infiltrating variety The demonstration, therefore, of a bronchial occlusion, particularly if it is ragged and irregular, should lead to

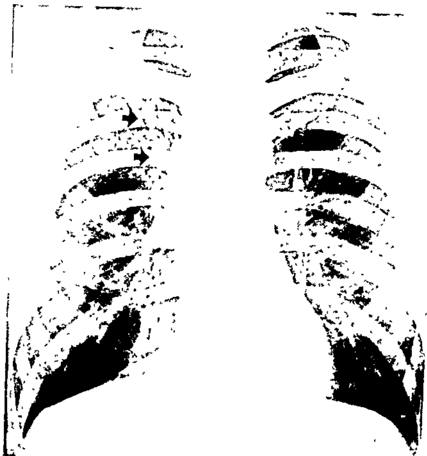


Fig 10—Infiltrating carcinoma, right upper lobe Note the beaded, nodular appearance of the shadows (arrows) which are highly suggestive of the carcinomatous nature of the process (From RIGLER, L G The roentgen signs of carcinoma of the lung Am J. Roentgenol 74 415–428 [Sept] 1955)

the diagnosis of carcinoma or at least should be sufficiently compelling to indicate the need for exploration. A diagnosis of unresolved pneumonia should not be made without undertaking laminagraphic or bronchographic demonstration of the bronchi

The presence of segmental, lobar or unilateral emphysema, especially in the expiratory phase, is indicative of partial bronchostenosis (fig. 12). This, of course, is far from definitive insofar as carcinoma is concerned, but if found in an individual past middle age it should certainly arouse the thought that this is carcinoma. Further investigation, therefore, with planigraphy or bronchography to determine the nature of the bronchostenosis is indicated. Very often, as will be observed later, the character of the occlusion thus observed may indicate clearly the fact that this is due to a carci-

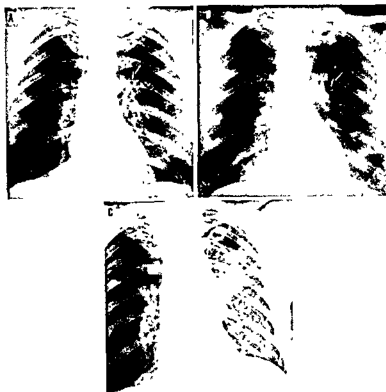


FIG 11—Carcinoma, left upper lobe bronchus (A) A normal hilum on first examination (arrow) and (B) the increase in the size of the hilum (arrow) on the second examination one year later are well shown (C) Less than a year later still, the mass increased sharply in size and the obstruction became complete The characteristic atelectasis of the lingular portion of the left upper lobe is shown Note the elevation of the diaphragm, the displacement of the heart and mediastinum to the left, and the great density within the segmental area of atelectasis (From RIGLER, L G X-ray diagnosis of cancer of the lung Postgrad Med *18* 361–373 [Nov] 1955)

noma of the bronchus The combination of emphysema and of an enlarged hilus almost invariably connotes carcinoma

Emphysema is best demonstrated by films made in expiration, especially if comparison is undertaken with films made in the inspiratory phase. If segmental there will be seen an area of increased radiability together with a diminution in the number of blood vessels The latter is most important, for changes in the chest wall may simulate emphysema If the process is lobar or involves a whole lung, changes in diaphragmatic motion and in position of the mediastinum will also be present The diaphragm on the affected side will not rise to a normal degree with expiration and the mediastinum will move to the normal side



Fig 12—Adenocarcinoma exhibiting mass in right main bronchus (A) The extensive atelectasis and pneumonitis of the right lower lobe is shown (B) On planigraphy, the tumor is shown as a positive shadow in contrast to the air within the right main bronchus (arrow) It is evident that air can extent into the upper lobe around the tumor mass itself, only the lower and middle lobes being occluded (From RIGLER, L G X-ray diagnosis of cancer of the lung Postgrad Med *18* 361–373 [Nov] 1955)

In some cases the emphysema will be visible in the inspiratory films but *will be exhibited more definitely in the phase of expiration.*

The same indications are present in atelectasis as in emphysema (fig 13). Obviously, atelectasis may be the result of a benign type of bronchostenosis but, again, in an individual past middle age in whom it has suddenly appeared, the suspicion that this is due to a carcinomatous obstruction of the bronchus is a first consideration. Here, again, planigraphy or bronchography may exhibit effectively the nature of the bronchostenosis and thus establish the diagnosis Atelectasis is best demonstrated in inspiration. It may be segmental, lobar or involve the whole lung When large areas are affected, the diaphragm will be elevated and the mediastinum displaced to the abnormal side

The demonstration of changes in the bronchial lumen can be made effectively in most cases by planigraphy (fig 14) Both posteroanterior and lateral planigrams should be made and a good technic is of great importance. When satisfactory, it is possible to delineate the bronchi of the first, second and third orders quite effectively The method is not very useful in lesions of the smaller bronchi. The demonstration by means of body section roentgenography *of a tumor as a positive shadow within the* bronchus, standing out in contrast with the air about it, is not rare in carcinoma and may be a crucial deciding point in determining the presence of the tumor. It may be difficult to distinguish between benign adenoma and a malignant tumor on



Fig 13—Carcinoma, right lower lobe bronchus Planigraphic study shows the air-filled lower lobe bronchus with the characteristic diffuse narrowing and stenosis which is typical for carcinoma The lower lobe is atelectatic (From RIGLER, L G The roentgen signs of carcinoma of the lung Am J Roentgenol 74 415–428 [Sept] 1955)

this basis, but at any rate, a sufficient indication of the neoplastic nature of the process is afforded to make surgery imperative. A cap-shaped indentation of the bronchial lumen either at its end or on one margin is also characteristic Finally, the demonstration of an elongated, somewhat irregular stenosis of the bronchus is indicative of malignant obstruction. In doing planigraphy, it is of great importance to get multiple sections at various levels to be certain that the stenosis is not being simulated by an angulation of the bronchus With these provisions in mind, however, it may be possible to demonstrate relatively small lesions in this fashion

In the smaller bronchi and occasionally, because of technical difficulties, in the major bronchi, planigraphy may be unsuccessful Under these circumstances the introduction of a contrast medium into the bronchi through a catheter localized to the area under suspicion may be a final method of definitive diagnosis, assuming that bronchoscopy has been unsuccessful in



FIG 14—Carcinoma, peripheral nodules, showing slow growth and bronchial origin (A) Size of nodule three years after first evidence of abnormality (B) Increase in size of shadow, moderate degree, one year later (C) Bronchogram shows the typical narrowing and stenosis of a branch bronchus of the lower lobe extending right up to the nodular lesion itself (arrows) Such a bronchographic demonstration is very helpful in making a definitive diagnosis (From RIGLER, L G The Detection of Cancer of the Lung Proceedings of the Third National Cancer Conference (June 4–6, 1956) Philadelphia, J B Lippincott, 1957, pp 515–520)

this regard Small branch bronchi may be delineated and the obstruction within them determined (fig 15). The character of the obstruction, whether exhibited by means of planigraphy or bronchography, is reasonably characteristic for carcinoma of the bronchus Such findings are of particular importance in the cases with apparent inflammatory infiltrates, unresolved pneumonias, etc., which are so often actually due to carcinoma and in which so much delay in diagnosis occurs. The demonstration by bronchography of a bronchostenosis, especially if the stenosis is irregular and elongated, should lead to the assumption that the pneumonic infiltration is due to carcinoma rather than a true pneumonia or any real inflammatory process In occasional cases the tumor may be seen as a filling defect in the opaque column within the bronchus.

Alveolar cell or bronchiolar carcinoma produces such distinctive roentgen signs that it must be considered separately Such tumors often begin with an irregular solitary peripheral shadow not markedly different from other spheroidal nodular lesions (fig 16) Frequently, however, several shadows are present which suggest metastases, but a primary tumor cannot be found The lesion enlarges slowly but commonly other shadows in the same or the



Fig 15—Carcinoma of the superior branch of the right middle lobe bronchus The displacement of the inferior branch by the mass in the middle lobe and the complete occlusion of the superior branch bronchus leading to the mass are well shown The upper arrow points to the horizontal fissure, the other arrows to the bronchi and especially to the occluded branch (From RIGLER, L G The roentgen signs of carcinoma of the lung Am J Roentgenol 74 415–428 [Sept] 1955)

opposite lung appear. These may be small beadlike projections along the vascular trunks which rapidly enlarge to form multiple small nodular masses In some cases, multiple shadows seem to appear spontaneously. They are usually not sharply defined nor as spherical as are found in other types of carcinoma The multiplicity of the lesions and the tendency to *involve both lungs is a distinguishing feature of the alveolar cell type of carcinoma* However it is difficult to distinguish from the more benign pulmonary adenomatosis both roentgenologically and pathologically

Bronchography in alveolar cell carcinoma frequently gives a striking and characteristic appearance The bronchi appear narrow, elongated, and unusually straight They resemble pieces of string No doubt this appearance

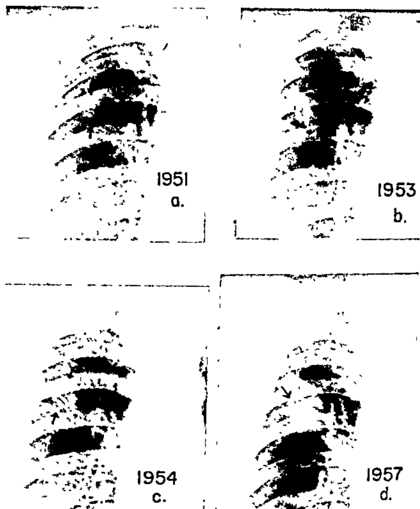


Fig 16—Alveolar cell (bronchiolar) carcinoma of the right upper lobe showing slow growth and progression from 1951 to 1957 while patient is asymptomatic Many alveolar cell carcinomas seem to arise from one focus in this manner, but eventually multiple foci may appear (From Rigler, L G · The Detection of Cancer of the Lung Proceedings of the Third National Cancer Conference (June 4–6, 1956) Philadelphia, J B Lippincott, 1957, pp 515–520)

is the result of compression by the surrounding alveolar infiltration. It is probable that pulmonary adenomatosis would produce a similar finding.

There may be other roentgen evidences of bronchogenic carcinoma which are either rare or appear later in the course of the disease.

1 The so-called Pancoast or pulmonary sulcus tumor arises in the apex of the lung as a solid shadow which soon extends toward the subclavicular area It is chiefly distinguished by the erosion of one of the upper three ribs and occasionally of the contiguous segments of the spine (fig 5)



Fig 17—Alveolar cell (bronchiolar) carcinoma of the left lower lobe The bronchographic findings are fairly characteristic and consist of extreme narrowing and rigidity of the branch bronchi thru the area of the tumor (From ZHEUTLIN, N, LASSER, E C, AND RIGLER, L G Bronchographic abnormalities in alveolar cell carcinoma of the lung Dis Chest 25 542–549 [May] 1954)

2 In other types of carcinoma of the lung, erosion of bony structures is uncommon but occasionally occurs especially in rapidly growing peripheral lesions When rib destruction is found, however, such lesions as mesothelioma of the pleura, primary tumor of the ribs, metastases and granulomas from fungus infection should first be suspected

3 The tumor occasionally appears as a large solid mass resembling a sarcoma The growth may be so rapid that it fills the hemithorax and displaces the mediastinum to the normal side

4 With bronchial obstruction, in addition to emphysema and atelectasis as described above, in occasional slow growing cases, all the signs of bronchiectasis may be found Most commonly, such tumors are found to be adenomas but in some cases, carcinoma is also found

5 Atelectasis may be massive producing a dense shadow in one lobe or in the whole hemithorax The heart, mediastinum and trachea will be displaced markedly to the involved side, and the diaphragm will be elevated It is notable that moderate treatment

either with radiation or by *bronchoscopic excision may produce striking* resolution of such densities by permitting aeration of the lung

6 Occasionally carcinoma exhibits itself as a mediastinal mass without apparent lung involvement. Such shadows are extremely difficult to distinguish from lymphoblastoma and *other mediastinal tumors* Here again, planigraphy or bronchography may exhibit the bronchial origin of the mass

7 Enlargement of the peribronchial and peritracheal lymph nodes is a common finding, usually late in the disease Most commonly parenchymal changes are present which help to distinguish it from other diseases producing lymph node masses Furthermore, in carcinoma, the enlargement is usually unilateral, although not invariably, as the disease may penetrate to the opposite side If parenchymal shadows cannot be found, it is impossible to distinguish such cases from lymphoblastoma or other lymphatic diseases. Even the presence of a parenchymal shadow, unless it is characteristic, is not distinctive.

8 The esophagus should be examined in all cases since displacement of this organ is often an early sign of deep involvement of the mediastinum Its significance is largely in relation to prognosis since such cases are usually inoperable

9 The pleura is usually involved late in the disease In rare cases, superficial tumors will produce an effusion even while the lesion is very small The presence of effusion often covers up the shadow of the lesion itself In such cases, aspiration with re-examination should be done If the amount of fluid is small, some help in demonstrating the lung lesion itself may be obtained by making anteroposterior films with the patient supine or in the lateral decubitus position Under these circumstances, the fluid usually will gravitate away from the base and exhibit a lesion previously hidden.

10 Extreme elevation and paralysis of one diaphragm without evidences of pulmonary atelectasis usually signifies that the tumor has invaded the mediastinum sufficiently to involve the phrenic nerve

11. Metastases occur more commonly in remote areas than in the lungs Aside from *the lymph node involvement, however, nodular metastases to other parts* of the same lung or to the opposite lung are not rare In a few cases, the metastases are miliary in type

The diagnosis of bronchogenic carcinoma is difficult at best. The roentgen examination should be thorough, including a variety of methods A careful weighing of the roentgen findings, together with all the other data, should permit a correct diagnosis in the vast majority of cases prior to operation Certainly the detection of an abnormality which can then be proved to be carcinoma by other methods is best accomplished by roentgen study.

CHAPTER 8

Treatment of Bronchogenic Carcinoma

By JULIAN JOHNSON, M.D.

THE SURGICAL TREATMENT OF CANCER OF THE LUNG has been the accepted form of therapy since Graham performed the first successful pneumonectomy for cancer in 1933. That patient is alive now 25 years later, although Graham, unfortunately, has died of the same disease This points very vividly to the fact that some cancers of the lung grow sufficiently slowly and/or remain localized so that they may be diagnosed at a stage when pulmonary resection is curative, whereas others metastasize so rapidly that the first symptoms of the disease are due to metastatic lesions rather than to the primary one In the 25 years since that first successful pneumonectomy, many patients have been operated on for this disease Unfortunately, long term survival for these patients has been the exception rather than the rule and many physicians and surgeons have become discouraged with the overall results of the treatment of this disease When one reviews the published data from large series of cases, it becomes apparent that the percentage of the patients who are admitted to the hospital with cancer of the lung who are alive and well five years later is in the neighborhood of 5 to 10 per cent (table 1). The surgeon has naturally been interested in trying to improve these results, and much thought and effort have gone into the methods by which such an improvement might be brought about. Of course, the figures of 5 to 10 per cent five year survival may be considerably improved if one selects the patients to be included in such an analysis. Unfortunately, more than one-third of the patients who are admitted to the hospital are never subjected to operation because of the evidence of inoperability at the time of admission Roughly one-third of those who are operated on are found to be nonresectable at the time of operation so that, in general, only 35 to 40 per cent of the patients admitted to the hospital are subjected to pulmonary resection As may be seen from the study of the statistical data presented from

the five year survival may approximate 70 per cent. Two methods of improving the five year survival data in carcinoma of the lung then naturally come to the surgeon's mind: first, an earlier diagnosis so that all or most of the patients may be operated on at the time when the tumor is apparently still

TABLE 1—*Five Year Survival—Carcinoma of Lung*

Senior Author	Year	Number Resected	% Op Mortality	% Resected Pt 5 Year Survival	% Tota Pt 5 Ye Surviva
Overholt	1956	234	15	22	7 6
Ochsner	1956		19 2	15	5 5
Watson	1956				
Radical Pneumonectomy		74	5 5	27 }26	
Less than Rad Pneumonectomy		42	*11*	*23 8*	
Gibbon	1956	145	23	21	8 4
Churchill	1958				
Pneumonectomy		127	10	24 }28	
Lobectomy		93	6 4	33	
Burford	*1958*	356	13	22	9
Johnson	1958	116	7 7	26 7	9

confined to the lung and, second, a radical extension of the operative procedure in the hope of removing the carcinoma which may have extended beyond the lung.

PROBLEM OF EARLY TREATMENT

The problem of making a diagnosis of carcinoma of the lung and getting the patient to operation before the tumor has spread beyond the confines of the lung is not a simple one Every physician experienced in this disease can remember patients who have had no symptoms whatever of the primary lesion but whose first complaint was precipitated by metastasis of the disease It is difficult to believe, therefore, that by any of the methods presently available it will be possible to pick up cancer of the lung of this type early enough to be helpful. An illustration of this phenomena may be pointed out by the fact that in our own series, 7 per cent of the patients admitted to the hospital were admitted because of a neurologic deficit, most commonly brain tumor, which is a manifestation of metastasis of the disease rather than from the primary tumor in the lung

Even though it must be admitted that there are some cancers of the lung in which there would appear to be little hope of picking up the lesion early, especially on the basis of symptomatology, nevertheless there are certain methods by which it would appear that we might improve the present record of getting the patient to the surgeon at a time when the tumor may still be successfully resected There are three approaches by which this may be brought about The first is that of routine chest x-rays in the group who are most susceptible to cancer of the lung This would be in men over 40 years of age There have been many campaigns carried out in this respect and a good bit of publicity has been carried on by various societies. There can be no question that many early cancers of the lung have been picked up by this means On the other hand there are also many people who have come to

operation and been found to be inoperable even though an x-ray of the chest may have been considered normal six months or a year previous to that time. Whether the total expense of having a chest x-ray taken on every man in the country over the age of 40 every six months would be adequately compensated for by the number of asymptomatic tumors picked up on such routine x-rays cannot be answered at this time. The information which is available at the present time suggests that 2 to 4 such tumors might be found in ten thousand cases Nevertheless, Churchill found the five year survival of the "survey" cases to be 42 per cent, as opposed to 28 per cent for the over-all group

The second method by which the patient with cancer of the lung might be gotten to the surgeon more quickly is that of the education of the general public to seek medical advice at the first symptoms of cancer of the lung This program has been carried on by the American Cancer Society and time alone will tell whether it will accomplish its purpose

The third method by which the patient may be brought to the surgeon more quickly is by education of the medical public in order to shorten the time between when a patient first sees a doctor because of symptoms of cancer of the lung and when he comes to surgery In one series studied, it was found that the patient delay, that is from the time that he had his first symptoms until the time he went to his first doctor, averaged three months, whereas the doctor delay, that is from the time the patient saw his first doctor until the time he was operated on, was five months With proper education of the general public and the medical public, it would seem that at least a portion of this average eight months' delay might be avoided

Extent of Surgery

The surgeon, impatient to try to improve his results in the surgical treatment of cancer of the lung, has become more and more radical in an effort to get around extrapulmonary extensions of the tumor in the hope of curing his patient It is, therefore, not at all uncommon at the present time for a surgeon to remove not only the lung containing the malignancy but also a portion of the chest wall, the diaphragm, the pericardial sac or even a part of the heart or great vessels in order to attempt to completely eradicate a malignant process In addition to this effort to get around a malignant lesion which can be visualized at the time of operation, it has also been proposed that by removing a large portion of the lymph node bearing area from the mediastinum, one might materially improve the results following resection for cancer of the lung. This proposal was made because of the fact that the five year survival has been known to be considerably better in patients who had no metastatic extension to the lymph nodes, than in those who had lymph node involvement. Thus, a prophylactic resection of the

lymphatics has been suggested on the same basis as it has been suggested in the treatment of cancer of the breast by radical mastectomy, as well as in the treatment of cancer of the colon by radical right colectomy or left colectomy Although radical mastectomy for carcinoma of the breast is almost universally accepted in this country, nevertheless the group in Edinburgh feel that not only has radical mastectomy not been shown to be superior to other forms of treatment but, in fact, that simple mastectomy followed by x-ray therapy in their hands produces results superior to those obtained by radical mastectomy alone. We are somewhat in the same position with carcinoma of the lung at the present time There are those who feel that a radical pneumonectomy is theoretically superior to the standard type resection and yet, up until the present time, there are no five year survival data to support this belief

Criteria for Surgical Exploration

In the surgical management of the patient with carcinoma of the lung, the question will always arise as to whether the specific patient is a candidate for surgical exploration. As will be shown in our statistical data later in this chapter, 43 per cent of the patients in our series were found to be inoperable for one reason or another and were not acceptable as candidates for exploratory thoracotomy. There may be considerable difference of opinion as to the factors which cause a surgeon to declare a patient inoperable. These will be discussed

The most common cause for rejection of a patient for exploratory thoracotomy is the evidence of distant metastasis. Some surgeons will agree to do palliative resections even in the presence of known distant metastasis; but we have not felt this to be justifiable.

We have considered a bloody pleural effusion as a contraindication to operation, or any pleural effusion if carcinoma cells can be found in the fluid

We have considered superior vena caval obstruction by a cancer of the right lung as a contraindication to operation

We have generally considered left recurrent laryngeal nerve paralysis as a contraindication to operation, particularly if the carcinoma is one of the left upper lobe bronchus Although we have occasionally operated on young individuals with this complication, I am not at all sure that we have ever had reason to rejoice over having done so.

Although I believe there is at least one five year survival in the literature following a radical operation for carcinoma of the apex of the lung with a Horner's syndrome, we have generally considered this as evidence of inoperability Although I think we, as others, have occasionally operated on such patients in the past, I do not believe that we have ever been able to completely excise the tumor.

Phrenic nerve paralysis is certainly a bad sign and may add to the accumulative evidence which might prevent exploration of a chest, but when seen as the only complication, we have not regarded it as positive evidence of inoperability. In a peripherally located tumor impinging on the mediastinum, the phrenic nerve may be caught in the tumor and still the entire tumor may be resectable. A tumor situated in one of the larger bronchi with phrenic nerve paralysis is much more likely to represent an inoperable malignancy

Evidence of or suspicions of invasion of the chest wall by a peripherally located tumor has not been considered evidence of inoperability in our series, since it is frequently possible to excise the tumor *in toto* by taking a portion of the chest wall with the specimen. This may also apply to the diaphragm and certain portions of the mediastinum

A patient may occasionally be turned down as a candidate for pulmonary resection because of inadequate pulmonary function or associated diseases—primarily cardiac When a patient's pulmonary function is very poor, it may be easy to make the decision to turn him down for pulmonary resection but, unfortunately, it frequently may be found that his pulmonary function is on the borderline In the presence of malignancy, it is difficult to turn him down for resection under those circumstances The result has been that many patients have died during the postoperative period because of inadequate pulmonary function The aggressive surgeon may take the point of view that since the end result is known if the malignancy is not removed, he is justified in taking any risk in going ahead with a pneumonectomy However, in many instances the pulmonary function is so poor that the experienced surgeon can say just as definitely that the result will be known if one lung is removed, and there is certainly no point in proving that to himself over and over again by taking a needless mortality in a patient who might live for many months if treated by other than surgical means

The question often arises in the surgeon's mind as to how extensive should be his search for evidence of distant metastasis before exploring a patient's chest with carcinoma of the lung Certainly we feel that if a patient has symptoms suggestive of distant metastases, these leads should be run down by all diagnostic measures However, it has been our experience that it is not profitable to put every patient through extensive studies looking for evidence of metastasis, in the absence of symptomatology For example, we have given up the custom which we followed for some time of having roentgenologic bone surveys on these patients, for the simple reason that it has been our experience that the pain appears a good while before the x-ray becomes positive in the presence of bone metastasis from carcinoma of the lung A much bigger problem has been whether or not to go ahead and operate on a patient who has some pain and yet the x-ray cannot demonstrate the metastasis to be present. Even though one suspects that metastasis is

present, one hesitates to postpone operation for fear that the pain may be on some other basis

It has been suggested that many thoracotomies might be avoided if every patient with carcinoma of the lung being considered as a candidate for thoracotomy were subjected to a bilateral scalene node biopsy. We have felt that this is not worthwhile as a routine procedure Not infrequently, one is in a position of feeling that a patient is inoperable or that he will not do well following a pulmonary resection without having positive proof of inoperability. Such patients we do subject to scalene node biopsy and occasionally will get a positive node which allows us to avoid a thoracotomy. The only patients on whom we routinely carry out scalene node biopsy are those in whom the x-ray suggests mediastinal lymph node enlargement When that is present, it seems probable that one can pick up a positive node by scalene node biopsy. If there is no evidence of lymph node enlargement on x-ray examination and unless we are going out of our way trying to find an excuse for not operating on a patient whom we consider on clinical grounds to be a poor risk, we do not do routine scalene node biopsies in our institution.

The patient who has borderline pulmonary function or a borderline cardiovascular status may be considered much more favorably for pulmonary resection if his lesion is situated peripherally where it may be possible to perform a lobectomy There is no question at all in our minds that the lungs are much more closely related to the patient's cardiac status than are the various portions of the gastrointestinal tract, for instance. It may be possible to resect the stomach or colon or gallbladder in a patient who has previously been in cardiac failure but to attempt to remove a lung in a patient who has been in frank cardiac failure has been, in our experience, a very hazardous procedure On the other hand, if the lesion is situated in the periphery where a lobectomy alone can be carried out, the possibility of carrying out a successful resection is certainly greatly increased and is a factor which may be considered in the evaluation of the patient being accepted for a pulmonary resection

Type of Surgical Procedure

Once the patient has been accepted for exploratory thoracotomy, the question then arises as to how aggressive the surgeon should be in removing the lung even though the tumor appears to have spread beyond the confines of the lung If the tumor is situated peripherally and is found to be stuck to the parietal pleura, it may be possible to resect that portion of the chest wall and remove the tumor *in toto*. We, therefore, have not considered this as evidence of inoperability unless the tumor is adjacent to and has invaded the vertebrae where the overlying chest wall cannot be resected. If the tumor has extended into the lymph nodes of the mediastinum or has invaded the

pericardium or other structures in the mediastinum, we have not regarded it as inoperable per se As long as it appears that we can get around the gross tumor and remove it entirely without actually having to cut through gross tumor, we have considered the lesion resectable If, on the other hand, in order to remove the lung it is found that it will be necessary to cut through gross tumor, leaving tumor behind in the mediastinum, we have considered such a lesion irresectable. It is, of course, true that one may occasionally find himself in the embarrassing position of having committed himself to a pneumonectomy before realizing that he will have to cut through tumor and leave some behind This is the exception, however, and is never done by us deliberately We have no hesitancy in opening the pericardial sac and dividing the great vessels inside the pericardial sac when it appears to be helpful in order to get around the gross lesion

There is some difference of opinion at the present time as to what type of pulmonary resection should be carried out on a more or less routine basis The term "radical pneumonectomy" was proposed by Allison in 1950 and it has been popularized in this country by Watson, as well as others It is favored by those who advocate it because it has been shown that in many instances cancer of the lung does spread through the lymphatic channels and it would seem reasonable to resect as much of the lymphatic-bearing area in the mediastinum as feasible, in the same manner as we do a radical mastectomy for carcinoma of the breast The lung is not a particularly favorable organ for an extensive lymphatic dissection inasmuch as there is a good bit of crossing of the mediastinum by the pulmonary lymphatics This can be said of the breast also since the lymphatics from the breast, particularly the medial border, go through the chest wall into the mediastinum It would certainly seem reasonable, therefore, on the basis of our present knowledge that in order to carry out a truly "cancer-type operation" it would be desirable to remove as much of the mediastinal tissue as possible The operation described by Watson under the term of radical pneumonectomy consists of starting the dissection at the apex of the mediastinum, dividing the mediastinal pleura from the chest wall, turning the mediastinal pleura and its contents downward and skeletonizing the trachea, esophagus and other important structures This dissection is carried down to the bifurcation of the trachea The pericardial sac is then divided at its junction with the diaphragm and the chest wall and the great vessels to the lung are divided inside the pericardial sac Then by dividing the main bronchus, the contents of the mediastinum at the carina can be freed from the contralateral bronchus, and the lung including the major portion of the mediastinal contents on that side, may be removed in one mass

Although we occasionally have done radical operations in order to get around gross tumor in the mediastinum, we have not used the "radical pneu-

monectomy" for the small lesion The primary reason for our not having utilized the "radical pneumonectomy" has been the fear that our operative mortality might increase in a manner to offset any gain that we might obtain by the more extensive resection. In the majority of our patients, we have carried out what we term a standard pneumonectomy which includes removing the lung without opening the pericardial sac and removing the major lymph nodes in the mediastinum adjacent to the lung. Most of the mediastinal pleura, however, is preserved In addition to this conservative "standard pneumonectomy," we have done a good many lobectomies for carcinoma situated in the periphery of the lung in recent years. Although in the figures to be reported later in this chapter, our lobectomies constituted only 17 of 116 resections up to five years ago, the number of lobectomies in recent years has increased to 25 or 30 per cent. In Churchill's most recent series lobectomies constituted 42 per cent of the resections

The question naturally arises then as to which is preferable, a radical approach to pulmonary resection as advocated by Watson, Allison and others, or the conservative approach to pulmonary resection which is being practiced by many surgeons throughout the country. As is so often the case in questions of this sort, there is no definitive answer to it at the present time. Watson has the largest series of patients operated on by the "radical pneumonectomy" technic more than five years ago (table 2). In a series of 116 resections, 74 were carried out by the radical technic, with a five year survival rate of 27 per cent, as opposed to 23 per cent five year survival rate for simple pneumonectomy and 25 per cent five year survival rate for lobectomy. He was encouraged to think that this small percentage difference in favor of "radical pneumonectomy" might be significant. However, when one considers that the good-risk patients were those who were subjected to "radical pneumonectomy" and when one considers the fact that being a good-risk patient would be more likely to put them in the five year survival bracket, it is hard to believe that these data are statistically significant.

In order to determine whether these data of Watson's were superior to those obtained by a standard resection, we have reviewed our data on carcinoma of the lung from 1939 to 1953. Three hundred and forty-four patients were seen in our hospital during that period (table 3). Fifty-six per cent

TABLE 2—*Watson—5 Year Survival Lung Cancer*

Resection	No	% Op Mortality	% 5 Year Survival
Radical Pneumonectomy	74	5 5	27
Simple Pneumonectomy	26	7.7	23
Lobectomy	16	18 7	25
Total	116	7 7	26

TABLE 3—*Carcinoma of Lung*
January 1, 1939-April 1, 1953

	Patients	%	5 Yr Survival	
			No	%
Clinical Diagnosis	344			
Explored	192	56		
Resected	116	34	31	26 7
Operative Mortality	9	7 7		
Pneumonectomy (Standard)	99	7	26	26 4
Less than Pneumonectomy	17	13	6	35

were explored and 34 per cent, or 116, were subjected to pulmonary resection The operative mortality was 7 7 per cent, which happened to have been exactly the same as that in Watson's series, so that the two groups seemed favorable from that standpoint to compare as to the value of radical resection, as opposed to standard resection Thirty-one of our patients survived five years, giving a five year survival rate of 26 7 per cent, essentially the same as in Watson's series (table 2) Certainly this would indicate no significant difference in the two methods of resection from the standpoint of five year survival It would seem probable, however, that if the more extensive procedure were carried out by the many thoracic surgeons throughout the country, the operative mortality would increase As a matter of fact, in a second three year period, Watson's group had their operative mortality jump from 5 5 per cent to 25 per cent for radical pneumonectomies If this can occur under such excellent circumstances as those supervised by Watson, it would seem likely that the mortality would be increased if radical pneumonectomy were generally accepted throughout the country At least we feel content in saying that to date radical pneumonectomy has not been proven to be superior to the standard resection as far as five year survival is concerned and that the surgeon who is accustomed to doing a standard pneumonectomy need feel no urgency in changing his technic to that of radical pneumonectomy

According to the concept of Allison and Watson, a good-risk patient who has a small lesion in the periphery of his lung would be subjected to a radical pneumonectomy in the hope of getting around any lymphatic spread which may have occurred in the mediastinum. Not only do we not do a radical pneumonectomy in such a patient but we feel that such a patient should be subjected to a lobectomy alone as opposed to a pneumonectomy. It is true that in our early experience we did a lobectomy only in those patients in whom there was borderline pulmonary function or some associated disease and we were fearful that a pneumonectomy might be too much for that patient. When we found, however, that 35 per cent of our patients subjected to lobectomy survived five years, we were encouraged to expand our lobec-

tomies to include all small peripherally located lesions. It is noteworthy also that Churchill's group with 42 per cent lobectomies had 33 per cent five year survival for lobectomies, as opposed to 24 per cent for pneumonectomies, giving 28 per cent for all resections Admittedly, it cannot be said that the standard resection is superior to a radical pneumonectomy provided the mortality of the latter procedure is kept within reason. Any surgeon who is thinking of embarking on a program of radical pneumonectomy for the small lesion, however, must see to it that his mortality is not increased by the utilization of that technic, since to date it has not been shown that the five year survival data can be improved by utilizing that technic

Significance of Blood Vessel Invasion

The surgeon likes to feel that he is the master of the situation and that by adopting a bold approach to disease, he may be able to get around the spread of the malignant process and increase the salvage in any type of malignancy. It is a great disappointment, therefore, to those of us who are surgically minded to find that radical pneumonectomy has not at least to date produced superior results It would seem inevitable that an occasional patient with spread through lymphatic channels might be cured by a radical pneumonectomy, whereas he would not be cured by a standard resection. It seems almost certain that that is true On the other hand, it is probable that the number of patients who would fall into that category would be so small as not to be statistically significant It would certainly seem that if cancer of the lung spread only through the lymphatics or chiefly through the lymphatics, there should be a real statistical difference between the results obtained by radical pneumonectomy as opposed to the standard resection. It was only within recent years that we have had some concept of the spread of cancer of the lung by other means and have been led to believe that spread through the blood stream is of much greater significance than that through the lymphatic channels.

Collier and his associates reviewed the pathologic data in our laboratory and found that blood vessel invasion could be observed by special stains in the surgical specimen removed at the time of operation in about 70 per cent of patients *with cancer of the lung In the study of the surgical specimens* it was found that blood vessel invasion was much more common in certain types of carcinoma than others. For example, in the anaplastic carcinomas, roughly 100 per cent were found to have blood vessel invasion, and in the epidermoid carcinoma—75 per cent; whereas in the low-grade tumors such as bronchial adenomas, only 1 of 11 had blood vessel invasion (table 4). Subsequently, 107 patients who survived pulmonary resection were reviewed and the five year survival figures compared with the presence or absence of blood vessel invasion, as well as the presence or absence of lymph node in-

TABLE 4—*Incidence of Blood Vessel Invasion in 224 Excised Lung Neoplasms*

Type	Number with Blood Vessel Invasion	Number without Blood Vessel Invasion	Percentage Blood Vessel Invasion
Epidermoid	73	44	63
Undifferentiated	37	0	100
Adenocarcinoma	42	6	88
Mixed	11	1	92
Cylindromatous	0	1	0
Bronchiolar	5	6	45
Carcinoid Adenoma	1	7	12
Total	159	65	71%

TABLE 5—*Carcinoma of Lung—Five Year Survival of 107 Patients Surviving Resection*

	Blood Vessel Invasion	Lymph Node Invasion	Resected	Alive 5 Years	%
1	+		71	4	6
2	−		36	27	75
3		+	53	8	15
4		−	54	23	43
5	+	−	28	2	7
6	+	+	24	2	8
7	−	+	10	6	60
8	−	−	26	21	81

vasion The data regarding lymph node involvement were taken from the routine pathology reports and did not constitute a special study as was the case with blood vessel invasion The data are shown in table 5 As will be seen, whereas only 6 per cent with blood vessel invasion survived five years, 75 per cent of those without blood vessel invasion survived five years This was in marked contrast to the influence of lymph node invasion since with lymph node invasion, 15 per cent survived five years, and without lymph node invasion only 43 per cent survived five years. It would appear obvious in these data that blood vessel invasion has much more influence on the prognosis of the disease than does lymph node invasion It would seem equally obvious that in the presence of blood vessel invasion, a radical pneumonectomy has nothing to offer the patient above and beyond that which could be expected from a standard resection It is of interest that in the patients in whom there was blood vessel invasion, the presence or absence of lymph node invasion was not significant. However, in the absence of blood vessel invasion, the presence of lymph node invasion was significant Obviously, the best results were obtained in that group in which there was invasion of neither the blood vessels nor the lymph nodes, in which event there was 81 per cent five year survival.

In consideration of these data, it would seem that if there is blood vessel invasion, the surgeon could be content with a conservative resection in the belief that if metastasis has already occurred at a distance, there is no particular point in trying to dissect out the lymph nodes of the mediastinum. On the other hand, we are perfectly aware that all cancer cells which spread through the blood stream do not survive to form metastases and, in fact, 6 per cent of the patients in this group who were shown to have blood vessel invasion survived five years Thus, from the standpoint of the individual case, one cannot afford to take an entirely pessimistic viewpoint even in the presence of blood vessel invasion. We do not have available at present a technic to determine the presence or absence of blood vessel invasion before the time of operation. That may be fortunate. Otherwise, we might inevitably become too pessimistic in this group of patients. If our data shown in table 5 are to be taken at their face value, it will be seen that in the absence of blood vessel invasion, 81 per cent of those without lymph node invasion survived five years, whereas only 60 per cent of those with lymph node invasion survived five years. It would seem obvious, therefore, that there would be an occasional patient in whom it might be possible to get around the last lymph node which might be involved by radical pneumonectomy, whereas that lymph node might be missed by a standard resection. We suspect, however, that what little salvage might be gained on this basis would more than be offset by the increase in the operative mortality if radical pneumonectomy were generally adopted

It is important that at this stage of our knowledge not too much in the way of conclusions be drawn from these data regarding blood vessel invasion. Certainly we believe that these data help us in giving a prognosis after the pulmonary resection has been carried out and study of the pathologic specimen has been made. However, it seems to us to not give the surgeon all the answers as to what to do at the time of operation We feel that in the small peripherally located lesion, the surgeon is justified in carrying out a lobectomy alone If the surgeon is anxious to carry out a lymph node dissection, a considerable mediastinal dissection can be carried out in addition to the lobectomy, but we have been content to do a lobectomy in these patients without an extensive mediastinal dissection. On the other hand, we do not know when blood vessel invasion occurs We have seen small tumors in which blood vessel invasion was present and the patients died within a few months of widespread metastasis On the other hand, we have seen quite large tumors in patients where a conservative resection was done and were quite surprised to find that the patients went on to a five year survival. In one instance, at least, a lobectomy was done thinking that it was a palliative resection, only to find that the patient survived five years In reviewing the slides in the light of our present information, we found that he did not have blood vessel invasion It may well be, therefore, that if there is no blood vessel invasion,

the patient may be cured by getting around the tumor locally. It cannot be denied, however, that there would almost certainly be an occasional patient who would also have lymph node invasion which might be entirely resected only by a radical pneumonectomy.

This new information does not help us particularly in trying to determine how extensive a lesion should be before declaring it irresectable. We have always taken the point of view that we should take the lung out provided we could get around the tumor without having to cut across it Even though we might remove large masses of lymph nodes from the mediastinum, we have gone ahead and removed the lung when we could do so without actually cutting across tumor The fact that we may have been too conservative in this regard is amply attested to by one patient operated on more than five years ago when only an exploratory thoracotomy was done on the basis that the lesion was irresectable When we found more than five years later that the patient was still alive, we were quite surprised in view of the fact that he had had no treatment of any kind, no chemotherapy or x-ray therapy. A review of his surgical specimen, however, indicated that he did not have blood vessel invasion It would seem to us, therefore, that this information certainly puts the pressure on the surgeon to try to get the gross tumor out if it is at all possible to do so, just on the basis that it might be one without blood vessel invasion and if he does get it out locally, the patient might be cured In essence, therefore, our philosophy regarding cancer of the lung at the present time is to do the big operation for the big tumor or for the centrally located lesion (that which can be seen by bronchoscopy) but to do the conservative operation, namely lobectomy, for the small peripherally located lesion

Summary

1 Pulmonary resection is the treatment of choice for bronchogenic carcinoma It should be possible to carry out this procedure with an operative mortality in the neighborhood of 10 per cent and a five year survival of approximately 25 per cent of those patients in whom pulmonary resection is possible

2 In the present series of 344 patients seen more than five years ago, 56 per cent were subjected to exploratory thoracotomy and 34 per cent underwent pulmonary resection, with a 7 7 per cent operative mortality and 26 7 per cent five year survival of those resected This represents 9 per cent of the total number of patients seen.

3 A standard pneumonectomy, which is removal of the lung and readily available mediastinal nodes, constituted 83 per cent of the resections, the remainder being lobectomies Gross extensions beyond the lung were resected when it could be done without cutting across gross tumor

4 The five year survival in this series utilizing standard resection technic

including lobectomies in some patients, was essentially the same as the be published results obtained in a series where radical pneumonectomy w utilized in the good risk patients.

5. The studies which indicate that blood vessel invasion is of much great importance than lymph node invasion in the prognosis of cancer of the lur may explain why the results of radical pneumonectomy have been disa pointing to date.

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CHAPTER 9

Miscellaneous Pulmonary Parenchymal Tumors

By COLEMAN B. RABIN, M D

RELATIVELY FEW TUMORS OF THE LUNGS originate in the pulmonary substance, or parenchyma, rather than in the bronchi. Some are distinctly epithelial growths in which a bronchial origin cannot be demonstrated. It is assumed that they arise from alveolar cells, but it cannot be denied that they may arise from the epithelium of the smallest bronchi They are usually called alveolar cell carcinomas Similar to these in some respects is the tumor which has been classified under the name, *pulmonary adenomatosis*, which also represents a growth of epithelial tissue. Although the natural course of pulmonary adenomatosis also ends fatally, the lesion does not exhibit all of the characteristics generally attributed to carcinoma

Malignant tumors also originate from the usual constituents of the interstitial tissue of the lung derived from the mesenchyme These are the sarcomas which arise from the connective tissue and the hemangiosarcomas which develop from the tissue of the blood vessels Benign fibromas, neurofibromas and myomas also occur in the lung, originating in the respective tissues which they represent They are extremely rare Quite common are the hamartomas which differ from the other growths in that they show evidence of congenital origin They are essentially benign

The parenchymal tumors pose a problem different from that of bronchogenic carcinoma Many of them are benign Those which are malignant are not apt to spread along lymphatic channels or cause bronchial obstruction The growths increase in size by expansion, spread from alveolus to alveolus, or they may involve the lungs in multicentric fashion The clinical and roentgenologic manifestations, therefore, usually differ from those of bronchogenic carcinoma The same holds true for the clinical course and the treatment

There is some difficulty in the classification of the neoplasms. For example, there is often difficulty in the differentiation of the alveolar cell carcinoma from bronchogenic carcinoma and from pulmonary adenomatosis. This has led to uncertainty concerning the true nature of some of the cases reported in the literature as alveolar cell carcinoma or adenomatosis There also remains a question as to the proper category in which the hemangioma, he-

mangiosarcoma or the lipoma should be placed. These tumors may be c genital in origin and belong to the general group of hamartomas.

In the present state of our knowledge, it is impossible to differentiate n of the miscellaneous parenchymal neoplasms from bronchogenic carcino until the growth has been removed for pathologic examination. Furth more, doubt often remains as to whether the tumor is entirely benign, which case its removal may not be required, or whether it is malignant a should be resected However, there are instances in which the clinical di nosis of a benign neoplasm is so reliable that operation may be avoided.

A description of each neoplasm will be given under its particular catego its manner of growth will be indicated and its clinical and roentgenologi features will be described Those features which differentiate the grow from bronchogenic carcinoma will be stressed, and the indications for ope tion and the extent of the procedure will be discussed

Despite the rarity of some of the growths, the opinions expressed in th chapter are the result of the author's personal experience with them Th reflect his own opinions concerning the pathogenesis of the tumors and t method of handling them This has been done because opinions as to the n ture of the tumors and their treatment vary with different individuals such an extent that a recital of all theories and opinions would make for co fusion We shall leave it to the reader to decide for himself which ideas a most acceptable, after he has made his own investigations

Alveolar Cell Carcinoma

The term "alveolar cell carcinoma" should be reserved for an epitheli new growth which will eventually metastasize to distant organs. Of cours the difficulty lies in determining whether the new growth would inevitabl metastasize if it is not removed, when in that particular case the tumor i resected and the patient remains well However, we are justified in classify ing the growth as a carcinoma if it has the same gross and microscopic char acteristics as those which have been known regularly to metastasize.

Grossly the tumor is well localized Microscopically, a connective tissu reaction is to be seen here and there at its periphery, demarcating it from th remaining lung as if by a capsule. However, the capsule is only rudimentary In many places the tumor cells at the periphery of the growth are seen to invade the surrounding lung parenchyma. Thus, the tumor grows by inva- sion as well as by expansion. The cells are quite large, and although they may appear rather uniform, atypism in size, shape and staining capacity of the cytoplasm and nucleus is present The nuclei are large in comparison to the cytoplasm of a normal cell, the nucleoli are often large and prominent, and mitoses may be found, although sometimes only after considerable search These characteristics stamp the growth as a malignant tumor. While



Fig 1—Gross specimen from autopsy of a 28 year old female with alveolar carcinoma involving a complete lobe

amount of mother-connective tissue between groups of them acinar formation is often present and may be the predominant feature

Since the tumor does not invade the larger bronchi, it usually produces no symptoms until it is quite large It may then involve almost an entire lobe of the lung and cause chest pain dyspnea and cough (fig 1) Rarely does it cause hemoptysis At any time during the course of its growth it may metastasize to the brain or bones and produce symptoms referable to these structures Clubbing is variable When marked, it may be associated with painful periosteal proliferation over the long bones near the joints, suggest-

ing arthritis However, movement of the joints is free of pain. Moreover, the *tenderness is demonstrated* to be located over the bones adjacent to the joints. In many instances there are no symptoms, and the neoplasm is found only on a purely routine examination of the chest In other cases the tumor is demonstrated at a routine x-ray examination in a patient whose only symptoms relate to the nervous system or who complains of bone pain. Fever, weakness, weight loss or anemia occur only when generalized metastases are present, or when the tumor has become large and undergone central necrosis.

The physical examination of the chest is *usually negative except in very large neoplasms When the tumor is of medium size* and a considerable portion of it extends to the very surface of the lung, a small area of dullness may be detected. Even a small portion of normal lung tissue distal to the tumor prevents the transmission of any dullness and gives rise to normal breath sounds. Rales are *practically always absent.*

The roentgen films disclose a fairly well demarcated, round or oval shadow However, the outline is not as sharp as in benign, encapsulated tumors, for there is always some infiltration of the adjacent pulmonary parenchyma by the alveolar carcinoma. The larger tumors may occupy an *entire lobe and displace the interlobar fissure in a bulging manner.* The tumor may also grow through the fissure into an adjoining segment of the lung. Sectional radiography with the rays parallel to the plane of the fissure may differentiate between a bulge of the fissure and growth of the tumor through it

Bronchoscopy is negative except for unusual cases in which there is displacement or bulging of a large bronchus by pressure of the neoplasm which lies outside its wall. Biopsies are not helpful as they are uniformly negative Neither have bronchial smears helped in the diagnosis *in the cases we have* observed, presumably because the tumor does not ulcerate into the bronchial tree.

The manifestations of the growth are the same as those of most cases of carcinoma arising from small bronchi. There is, however, less tendency to involvement of the lymph nodes, or extension *into the chest wall and involvement* of the overlying ribs There is also less tendency to hemoptysis. In the absence of these manifestations, a localized neoplasm arising from a small bronchus cannot be differentiated clinically from an alveolar carcinoma. That the tumor is malignant is indicated by the absence of an extremely *sharp circumscription of its border and the tendency* to lobulation of the shadow. The final diagnosis depends on the pathologic examination. This shows the bronchi to be entirely free of the tumor which has a more or [illegible]

bronchial rather than an alveolar origin.

In the past we have used the term *parenchymal neoplasm* for all of the

round tumors in which no bronchial origin could be determined grossly The term alveolar carcinoma was avoided because of doubt concerning the presence of epithelial cells in the wall of the alveolus However, it appears safe to say, on the basis of studies made in embryos and on specially prepared material in the adult, that there do remain remnants of an epithelial lining in the form of cells here and there in the alveolus Since neoplasms conceivably can arise from these cells, the term "alveolar carcinoma" is justified. However, it is impossible to be certain that the tumor may not arise from the cuboidal cells of the tiniest bronchi in many instances Nevertheless, the term alveolar carcinoma is applied to those epithelial neoplasms arising in the pulmonary parenchyma which show no definite evidence, grossly or microscopically, of originating in the epithelium of the smallest bronchi

Since there is no great tendency for the tumor to spread along the bronchial walls toward the lung root, I would consider lobectomy the operation of choice. Where the tumor is situated near the root of an upper lobe, so that its complete eradication by lobectomy appears to be difficult, the remainder of the lung can still be spared if a sleeve resection is performed The main bronchus is then removed together with the upper lobe, and the lower lobe or intermediate bronchus is anastomosed to the trachea or to the short stump of the main bronchus It is wise to perform a lymph node dissection because of the possibility that a few neoplastic cells may be present within the nodes Pneumonectomy may be avoided if the tumor has grown through the fissure to involve only a small portion of an adjacent lobe This portion may be removed by segmental or local resection together with the involved lobe

ADENOMATOSIS

The term, *adenomatosis* is applied to a rare pathologic entity in which the pulmonary alveoli appear to be lined by hyperplastic, tall, columnar epithelium The cells are somewhat similar to the columnar epithelium lining the bronchi, but they appear larger and are not ciliated The proliferating cells may show few mitoses They lie on the basement membrane of the alveolus but may appear to be stratified since some of the cells project into the lumen of the alveolus in a papillary manner Large globules of secretion are seen within the cells The secretion may fill the alveoli.

The gross appearance is usually that of consolidation of the lung rather than that of a neoplasm The cut section appears homogeneous, dry, gray and firm as in gray hepatization The architecture of the lung is preserved and the septa are seen to be undistorted The lesion may be confined to a single lobe of the lung and either the whole or part of the lobe homogeneously involved A similar change may be present in one or more of the remaining lobes as in lobar pneumonia In other cases, the individual lesions are much smaller but the process is widespread (fig 2) The disease then involves groups of lobules throughout the lungs with relatively normal lung



Fig 2—Photomicrograph of lung with multicentric foci of pulmonary adenomatosis

tissue between the lesions The bronchi are undisturbed, and in classical cases the lymph nodes are not involved

An appearance such as this has been described in sheep in South Africa under the name of jagziekte. This disease has been thought to be due to a virus infection. However, the entire entity is not clear—in sheep any more than it is in humans. We know of no counterpart in the pathology of inflammatory diseases of the lungs in humans, and it appears quite certain that the condition is really in the nature of a new growth.

Because of the occurrence of the lesions in different parts of the lung

without any connection with each other, and because of the absence of distinct evidence of lymphatic dissemination in the lungs, a multicentric origin is postulated However, spread by aspiration through the bronchi may account for the involvement of widely separated portions of the lung The microscopic picture suggests that the local spread of the disease, within each of the affected parts, is from alveolus to alveolus through the pores of Cohn

Lymph node involvement has been recorded However, differentiation of adenomatosis from some cases of bronchogenic adenocarcinoma is difficult, so that the diagnosis of adenomatosis may have been erroneous The bronchi must be examined most carefully If they are involved, the possibility of adenomatosis should be excluded If this precaution is observed it is possible that no cases of lymph node involvement or of distant metastases will be found in adenomatosis

Clinically, adenomatosis is characterized by an insidious onset The first symptom is cough, frequently followed later by the production of large amounts of rather clear, thin sputum This characteristic type of sputum occurs when the disease is fairly extensive The patient then brings up mouthfuls of clear, watery material which looks like saliva but it is not apt to be frothy That the material is not saliva becomes evident to the physician when he is present during the coughing spell which produces the sputum At this time it is noted that the fluid is coughed up from the bronchi and does not originate from the mouth As the disease progresses to involve a large portion of the pulmonary parenchyma, dyspnea supervenes and clubbing may be quite prominent Eventually death takes place from respiratory failure because of the replacement of the lung by the spreading process

The roentgen appearance varies One of the characteristic manifestations is a homogeneous shadow of consolidation of a large part of one of the lobes, similar to that of lobar pneumonia The disparity between the roentgen findings which suggest pneumonia, and the clinical picture of a patient who appears comfortable, well and without fever, is quite striking This clinical and roentgenologic picture suggests mineral oil pneumonia However, there is usually no history to indicate aspiration of mineral oil

In the later stages, evidences of cavitation may be seen Cystlike cavities filled with secretion are not uncommon in the pathologic specimen However, these are not recognizable on the film if they are filled with secretion When the contents are emptied through the bronchi one or more cavities with or without a fluid level are visualized

In one of my patients in whom there was a shadow of diffuse consolidation of a lower lobe I considered the process to be due to aspiration of mineral oil. For many years she had been taking large doses of the oil before retiring After two years of observation, during which time there had been a slight increase in the area of involvement, she began to expectorate large amounts



Fig 3—Gross specimen of lung with hamartoma showing scalloped border and flecks of calcium

they have no capsule, and therefore fall into this category. However, these tumors, when in pure form and not mixed with other elements, had best be designated according to the tissue of which they are constituted even though they have no capsule and are, in reality, hamartomas. This suggestion is made because they represent unusual forms and their designation has been of long-standing On the other hand, when other elements coexist, these tumors also should be called hamartomas

The concept that the hamartoma grows with the body in parallel fashion is not true. We have all observed some of these cartilaginous tumors to grow

in size during adult life. Because of the conception of the hamartoma as an embryonal malformation, it has been thought that the tumor is always visible in early life This is also not true We have observed three cases in which roentgen films were negative two, three and seven years before the tumor was discovered. While it is undoubtedly true that the cell-rests were present at birth, their growth and development did not occur until much later The fact that a tumor makes its appearance late in life does not necessarily mean that it is not a hamartoma

Hamartomas arising in the bronchi, and chondromas of bronchial origin will not be discussed in this chapter The only ones to be considered here are those in the pulmonary parenchyma Because these are not connected with the bronchial tree, there is no cough or hemoptysis They do not cause pain even if they are situated beneath the pleura Since there are no symptoms, the tumors are not discovered during life except at a routine x-ray examination of the chest, or at an x-ray examination performed when the patient complains of symptoms from some other disease of the respiratory tract In the latter instance, the related respiratory symptoms may lead to error in the diagnosis

Since the tumors are usually quite small and do not involve the bronchi, they do not give rise to any abnormal physical signs Even if they are large, there is usually enough air-containing lung between the major part of the growth and the chest wall to mask its presence on percussion or auscultation The diagnosis depends entirely on the interpretation of the roentgen findings

The shadow cast by the growth is often described as coin-shaped Most commonly it varies in size from a few millimeters to 4 to 5 cm in diameter Larger ones, measuring up to 10 or 15 cm in diameter are extremely rare The neoplasms are practically always round The unusual, larger ones may be oval-shaped or lobulated With rare exceptions the border of the shadow is quite smooth and extremely sharply demarcated, thus differing from primary carcinomas of the lung which in our experience rarely if ever show such a sharply demarcated circumference On the other hand, an extremely sharply demarcated circumference may be present in certain metastatic neoplasms This occurs particularly in sarcomas and melanocarcinomas, and occasionally in hypernephromas

A roentgen appearance similar to that of the hamartoma is encountered in tuberculosis, either in the form of a tuberculoma or a well encapsulated fibrocaseous nodule The latter are often irregular in shape This serves to differentiate them from most hamartomas Occasionally, small hamartomas appear irregular despite the sharply demarcated border When a lesion of this type is situated in the upper lobe differentiation from a fibrocaseous nodule is often impossible Hamartomas containing a considerable amount

of bone appear quite dense This is also true of old fibrocaseous nodules whi contain a considerable amount of calcium. The round, sharply demarcat hamartoma casts a shadow identical with that of the encapsulated lesic of coccidioidomycosis. In patients who have been in the region where co cidioidomycosis is endemic, the differentiation of these two lesions is im possible from the findings on ordinary films

From what has been stated concerning the roentgen appearance, it is evi dent that the usual difficulty lies in differentiating the hamartoma from in flammatory and metastatic lesions In the case of the former, the differen tiation is usually not of immediate clinical concern. It is important, however to determine whether there is any evidence of a primary tumor which migh be responsible for a metastasis. It is necessary to find out whether a lesion which might have been considered innocent, such as a mole or a cellular fibroma, had been removed The skin and the extremities must be examined carefully for a possible primary source of the tumor and an intravenous pyelogram should be made A careful roentgen study should be made to exclude the presence of other nodules in the lungs.

In rare instances, primary bronchogenic carcinomas, between 2 and 4 cm. in size, present fairly well demarcated shadows on the film, so that one should hesitate to exclude a malignant tumor when a benign lesion, such as a hamartoma, is suspected Every effort should be made to obtain previous films for comparison. A film made five or ten years before may have been reported as negative and review show the tumor to have been present at that time. This will suffice to exclude the possibility of a malignant neoplasm But it should be borne in mind that a primary bronchogenic carcinoma can remain unchanged in size for a year, and perhaps up to two or three years, before it shows evidence of growth. On the other hand, the possibility of a hamartoma cannot be excluded because a film made several years previously failed to show the growth Only the microscopic anlage may have been present at that time, and thus would not be visible on the films

The shadow of a peripheral type of bronchial adenoma arising from a very small bronchus, or one in which no bronchial origin can be demonstrated, is exactly the same as that of most hamartomas on ordinary roentgen films. Since the adenoma grows slowly, it cannot be excluded from consideration even though it is known to have been present for many years Because of its malignant potentiality, it should be removed.

From what has been said concerning the appearance of the hamartoma on conventional films and the fact that there are lesions which present a similar roentgen picture, the suspicion of a hamartoma carries with it the possibility of other, more important lesions which require surgical treatment It therefore becomes necessary to resect the lesion unless a special characteris-

tic can be found which will stamp the abnormality as an innocent hamartoma.

A considerable proportion of the hamartomas contain bone in sufficient quantities to be demonstrated roentgenologically. The density caused by the calcium in the bone is arranged in a rather characteristic pattern The bone is present in the form of smaller or larger islands, diffusely scattered throughout the tumor. While occasionally visible on ordinary films, the calcium is more frequently demonstrable on overexposed films or on those made with the Bucky diaphragm. The pattern is most clearly discerned on sectional radiography. On the sections, the shadow appears to be stippled throughout its extent with extremely fine densities In other cases, particularly in the bigger hamartomas, irregular, larger densities are visible throughout the growth When this characteristic pattern of calcification is seen, there should be no hesitation in designating the tumor as a hamartoma One is then justified in withholding surgical treatment

The pattern of calcification of the hamartoma differs from that of the tuberculoma, in which there is a dense calcific deposit in the exact center of the shadow The central calcific deposit of the tuberculoma may be surrounded by concentric rings of calcification, or there may be a central area of apparent lucency surrounded by one or more rings of calcification The fibrocaseous nodule or a calcified coccidioidoma may appear homogeneously dense because of its high calcium content. This appearance may also be presented by the hamartoma Operation is not indicated in any of these cases

A blocked tuberculous cavity may show a dense calcific deposit characteristically situated along one part of its circumference It is generally best to remove such foci Carcinomas may grow about an old, calcified tuberculous focus The presence of the calcium may suggest a benign lesion, but its location, either in the periphery or off center in the nodule, or the presence of two or three small calcific foci is unlike the distribution of calcium in the hamartoma The differentiation should present no difficulty

The only condition in which I have noted the characteristic pattern of calcification seen in hamartoma has been metastatic osteogenic sarcoma Here the distribution of the bone within the sarcomatous metastasis is quite similar to the distribution of the bone within the cartilaginous tissue of the hamartoma The roentgen picture is therefore the same The diagnosis depends on locating the primary source of the osteogenic sarcoma

In summary, then, it may be said that the only cases in which it is safe to make a diagnosis of a hamartoma are those in which a characteristic pattern of calcification can be demonstrated and in those which have shown little or no growth over a period of several years In other instances, unless it can be definitely shown that the disease is inflammatory, operative removal is indicated

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Diffuse Form of Hamartoma

The hamartoma may occur in an unusual form Instead of forming a localized growth, there may be simply a replacement of an entire lobe of the lung or a large portion of a lobe by dense tissue. On microscopic examination the lesion is seen to consist largely of loose connective tissue resembling mesenchyme. A variety of structures, rudimentary alveoli and bronchi, glandlike formations of cuboidal epithelium, cartilage and bone, are scattered throughout the matrix of connective tissue. It is evident that we are dealing with a malformation The difference between this and the ordinary form of hamartoma appears to be largely one of maturity of its elements. Those which form the diffuse type of hamartoma appear to be less mature.

This type of hamartoma has been found in children. As in the case of other important malformations, it may exist in combination with other congenital abnormalities When the disease is extensive enough to involve a major portion of lung, it can produce dyspnea. Dullness and alteration of the breath sounds are then present, and lead to its detection The roentgen appearance is simply that of consolidation of a portion of the lung The possibility of a diffuse form of hamartoma is to be considered in a child when there is a persistent shadow of consolidation, not associated with fever or atelectasis If one could be certain of the diagnosis, no treatment would be indicated. However, exploratory operation has been performed because of the possibility of a neoplasm or some other condition requiring surgical treatment.

Other Benign Neoplasms

Other benign neoplasms are rare. They are fibromas, lipomas, hemangiomas, lymphangiomas, myomas and neurofibromas We have seen examples of encapsulated fibroma, lipoma and neurofibroma Because of their encapsulation, one must consider them as true neoplasms rather than hamartomas. However, the lymphangiomas and hemangiomas have not been encapsulated, and consequently should be considered among the hamartomas Some myomas probably also fall into this category

These tumors are so rare that few have been described I personally, have had experience with only one or two in each of the categories mentioned In the two lipomas which we have seen the shadow was quite faint even though the lipomas were between 6 to 8 cm in diameter. The hemangiomas were poorly demarcated. They looked more like inflammatory lesions The remainder of the tumors were sharply circumscribed and round, and measured only 3 to 4 cm in diameter. The sharp circumscription of the border is indicative of a benign lesion Nevertheless, I would recommend operative treatment in most cases because of the possibility of a malignant neoplasm. Exceptions may be made if the tumor has been present for many years, or if the patient's general condition is poor.

SARCOMA

Sarcomas of the lung should not be confused with those which arise from the connective tissue of the pleura covering the lung The subpleural connective tissue is highly specialized, and while it gives rise to sarcomas, the latter have the appearance of fibrosarcomas or cellular fibromas Despite their cellularity, these tumors are essentially benign On the other hand, the sarcomas which originate from the connective tissue within the lung substance are malignant Two types of sarcoma have been observed These are the spindle cell sarcoma and the hemangiosarcoma

Spindle Cell Sarcoma

Spindle cell sarcoma of the lung usually grows rapidly It produces no symptoms until it is large enough to cause dyspnea or involve the pleura, in which case it causes pain We have observed a case which eroded the bronchus and produced hemoptysis

By the time the tumor is recognized, it usually has attained large size It then presents itself on the roentgen film as a sharply demarcated, large, round or lobulated shadow If it is perfectly round, its sharply demarcated border suggests the presence of a cyst, and if situated in the mesial portion of the chest, it may be confused with a mediastinal cyst An increase in the size of the roentgen shadow may be noted within a matter of several weeks However, we have seen one case in which the tumor measured only about 6 cm in diameter and the growth had occurred slowly over a period of three years In a recently observed case, the huge tumor was situated immediately over the diaphragm and was associated with a small effusion in the free pleural cavity. The appearance then simulated an infrapulmonary lesion A film made a year previously was negative although the tumor was enormous when first seen

As in other spindle cell sarcomas, there is a tendency to hemorrhage and necrosis In the case mentioned above, aspiration yielded 500 cc of old blood At first it was thought that the patient had a loculated hemothorax which was largely clotted The correct diagnosis was made when the aspirated material was examined pathologically

Despite the rapid increase in size of the tumor and its tendency to involve pulmonary veins, the growth remains quite localized It can therefore be resected even when huge Two of the cases we have observed have remained well for many years after resection In a third case, the tumor proved resectable even though it was immense Despite the apparent high grade of malignancy of these growths, it would appear that a good many of them should be cured by surgery

adenocarcinoma, cylindroma or carcinoid tumor and malignant adenoma The term "cylindroma" was first applied by Billroth in 1859 to a tumor of the paranasal sinus invading the orbit. The similarity between these tumors arising in the accessory nasal sinuses and those in the tracheobronchial tree was recognized and the same term used for these tumors It was thought that they occurred wherever major or minor salivary glands or simple mucous glands were found In recent years as more data have been collected concerning the carcinoid and cylindromatous adenomas it has been increasingly apparent that there is a definite difference between these tumors in regard to their location, degree of malignancy and response to treatment. In spite of their differences, however, these two tumors are closely related and cause similar clinical manifestations. Because of differences in natural history and prognosis, it is of importance that these tumors be recognized and a sharp distinction made between them and bronchogenic carcinoma.

Theories of Origin

There have been many theories suggested to explain the origin of adenomas and the variations seen in the cellular pattern. Heck (1916) advocated origin from embryonic buds or nondeveloped foci of lung anlages Wessler and Rabin believed that the adenomas originated in the duct epithelium of mucous glands because (1) the tumors are covered by intact epithelium and lie on an uninterrupted basement membrane, and (2) their cellular elements do not resemble elements of mucous glands and no apparent transition from normal mucous glands could be seen Hamperl and Stout believed that the adenomas arose from the peculiar cells known as "oncocytes" or "pyknocytes" which are found in mucous and serous glands and their ducts. Crafoord and Lindgren placed the bronchial adenomas with the mucous and salivary gland tumors recognizing their characteristic slow growth as well as a tendency toward "local malignancy" i e. local invasion of surrounding structures. Because of a certain resemblance of some of the adenomas to fetal lung tissue, Womack and Graham suggested that they were associated with failure of the embryonic buds to develop into normal structures and termed these tumors "mixed tumors" of the lung. They believed that they were formed of both entodermal and mesodermal elements and regarded them as potentially malignant They considered them similar in behavior and origin to the mixed tumors of the parotid gland After years of controversy it is now generally acknowledged that bronchial adenomas have their origin in the mucous glands and their ducts in the bronchial walls.

Malignancy

For many years there was considerable disagreement over the malignancy of the adenomas Some writers believed them entirely benign, some considered them benign but capable of undergoing a malignant change, and

still others considered them to be malignant tumors which grow very slowly and metastasize late in their course There is now ample evidence that these tumors do grow slowly, are locally invasive and also may metastasize to lymph nodes, mediastinum, vertebrae and liver Numerous authors have reported cases of metastatic adenomas and have shown that the adenomas of the cylindromatous type are much more likely to metastasize than the carcinoid adenomas McBurney, Kirklin, and Woolner reported 87 instances of bronchial adenoma with metastases stating that 10 per cent of all adenomas metastasized They believe that the histopathologic picture may indicate that a given adenoma may have metastasizing qualities None of the adenomas in the Mayo Clinic series that had perfectly regular carcinoid pattern and little or no pleomorphism or mitotic figures metastasized distantly. In two cases such adenomas did metastasize to lymph nodes In those tumors that metastasized distantly the carcinoid pattern was not orderly. Pleomorphism, mitotic figures and irregular cell pattern were more frequent Adenomas of the cylindromatous type were three times as likely to metastasize as those of the carcinoid type In our series of 37 cases four showed evidence of local invasion and three had distant metastases Of the three patients who had distant metastases, i e. metastases to cervical nodes, diaphragm or contralateral lung, two patients had tumors which were histologically of the cylindromatous type

Incidence

Adenomas are said by various authors to comprise between 6 and 10 per cent of all primary lung tumors. Only 3 per cent of our 1,215 primary bronchial tumors were adenomas, perhaps reflecting the increased incidence of bronchogenic carcinoma Adenomas are found more frequently in women than in men in contrast to bronchogenic carcinoma In our series, adenomas were found almost twice as frequently in women as in men (23 women and 14 men) The average age of our patients when seen for treatment was 42 years with the majority of the patients in the 30 to 39 year age group (fig 8). The greatest number of these patients noticed the onset of symptoms between the ages of 20 to 30 years and had had symptoms for an average of six years at the time they were first seen These figures do not differ greatly from larger collected series of adenomas but are strikingly different from the figures for bronchogenic carcinoma There were 35 white patients, one American Indian and one Negro in this group The youngest patient was 14 years old while the oldest was 69

Location

Adenomas are most frequently found arising from the bronchial wall of one of the major bronchi For this reason a very high percentage are visible by bronchoscopic examination and accessible for biopsy In our series so

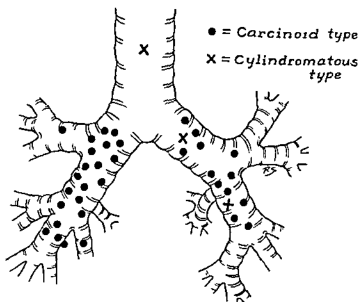


Fig 1—Location of adenomas in the tracheobronchial tree (37 cases)

per cent were located in the major bronchi in which they could be seen by means of bronchoscopy (fig. 1). Since the glandular elements from which the adenomas arise are found as far out into the bronchial tree as the cartilage extends, i e. to a diameter of 1 mm., theoretically tumors arising in these glands may be found quite far out in the periphery of the lung Maier found 10 per cent to be located peripherally However, these tumors are most frequently seen in the major bronchi probably because the glands are more numerous in the larger bronchi In our series only three tumors were seen on roentgenograms as pulmonary nodules, i e. a peripheral nodule surrounded by lung parenchyma. The cylindromatous type is more likely to occur near the coryna or in the trachea while the carcinoid adenoma rarely if ever involves the trachea.

Gross Pathologic and Bronchoscopic Appearance

Grossly the adenoma is usually found as a polypoid or sessile, lobulated mass protruding from or through the bronchial wall. The intrabronchial portion frequently constitutes only a small part of the tumor mass with the major portion being in the peribronchial region. At the time of operation the tumor may be felt as a soft to moderately firm peribronchial mass which can be separated without great difficulty from the surrounding lung and mediastinum but with a very firm bronchial attachment Through the bronchoscope the adenoma may ... intra-
bronchial structure covered l
vascularity of these tumors

even exsanguination has been reported following biopsy. For this reason, many surgeons prefer not to biopsy any tumor that has the typical bronchoscopic appearance of an adenoma The cylindromatous adenomas seen in the trachea may show more evidence of ulceration and be more diffusely situated over the tracheal wall There may be marked bronchiectatic changes and destruction of lung tissue due to the presence of chronic infection distal to partial or complete obstruction of the bronchus

Microscopic Appearance

The carcinoid pattern is found microscopically in 90 per cent of the adenomas These tumors are composed of small uniform cuboidal cells which contain a moderate amount of very finely granular eosinophilic cytoplasm and are arranged in strands, sheets or in acinous formation (figs 2 and 3). The nuclei are round or oval, deeply staining and usually centrally placed There is little pleomorphism and mitoses are absent in the well differentiated carcinoid pattern These tumors resemble the carcinoid tumors of the small intestine but argentaffin granules have rarely been demonstrated

The cylindromatous type of adenoma is composed of small cells with darkly stained round or oval nuclei (fig 4). There is a moderate amount of clear cytoplasm present The cells are arranged in branching masses forming tubules or in groups forming irregular spaces which are filled with mucoid secretion. Mitoses are rarely seen except in actively infiltrating areas This tumor is much more likely than the carcinoid type to invade locally as well as to have distant metastases The only late deaths in our series were in two

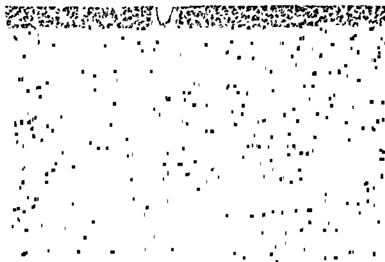


Fig 2—Photomicrograph of a typical carcinoid adenoma (× 150)

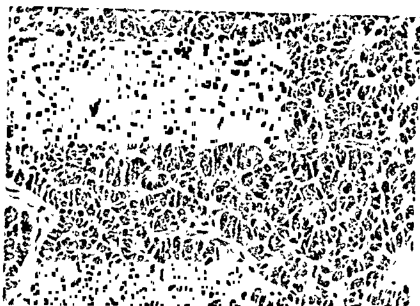


Fig 3—Higher magnification of the same carcinoid adenoma (× 400)

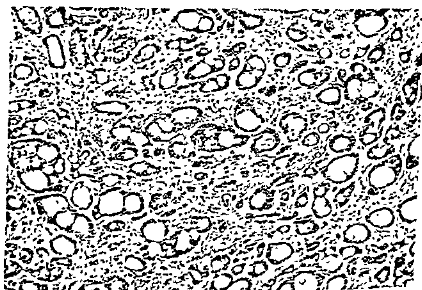


Fig 4—Photomicrograph of a cylindroma of the trachea (× 150)

patients who had the cylindromatous pattern. In a series of cases reported by Enterline and Schoenberg cylindromata were found to have caused death seven times as frequently as the carcinoid type and to have recurred seven times as frequently.

Clinical Signs, Symptoms and Diagnosis

The clinical signs and symptoms associated with the bronchial adenoma are due either to the extreme vascularity of the tumor or to the obstruction of the trachea or bronchus caused by the tumor mass (table 1). Hemoptysis may be the predominant symptom occurring suddenly in considerable amounts and unassociated with other symptoms In our series although hemoptysis was the predominant symptom in almost a third of the patients, signs and symptoms of suppurative disease with or without hemoptysis were more frequently found.

The symptoms due to tracheal or bronchial obstruction vary with the location of the tumor and the degree of obstruction (table 2). A wheeze due to a partial obstruction is not uncommon, particularly in the case of tumors located at or near the coryna As the obstruction becomes more complete and drainage to the affected lung is impaired, chronic infection develops distal to the tumor site, and the clinical picture becomes that of chronic suppurative disease of the lung with productive cough, fever and chest pain. This was the most frequent symptom complex in one-half of the patients in our series Although the bronchial adenoma may be present as a silent lesion, in only three of the 37 patients was this the case. The tumors in these patients were found as asymptomatic pulmonary nodules on chest roentgenograms

Table 1—*Predominant Symptom in 37 Patients with Bronchial Adenoma*

Suppurative Disease (Fever, productive cough)	18
Hemoptysis	10
Bronchial Obstruction	5
Asymptomatic	3
Cough	1

Note Suppurative disease of the lung associated with bronchial obstruction dominated the clinical picture in almost one half of the patients

Table 2—*Signs and Symptoms in 37 Patients with Bronchial Adenoma*

Hemoptysis	20
Fever	20
Purulent Sputum	19
Cough	18
Chest Pain	8
Increasing Mass by Roentgenogram	7
Dyspnea	6
Wheeze	5
Weight Loss	2
Asymptomatic Pulmonary Nodule	3
Clubbing of Fingers	1

Note Hemoptysis with or without symptoms of suppurative disease of the lung was the commonest single clinical finding

The diagnosis of a tracheal or bronchial adenoma is usually not difficult The long duration of symptoms suggestive of tracheal or bronchial obstruction associated with hemoptysis or chronic localized suppurative disease of the lung may lead the clinician to suspect the presence of an adenoma. The tumor may be seen by means of bronchoscopic examination in a high percentage of cases (80 per cent of our series) and a biopsy taken. The hazards associated with bleeding following biopsy have already been mentioned The surgeon should also be aware of the difficulty in making an accurate diagnosis pathologically on a small biopsy specimen. There is not only considerable difference between the microscopic appearance of different tumors but also in the appearance of different areas of the same tumor. For this reason a pathologic diagnosis made on a biopsy specimen should be accepted by the surgeon only if it is consistent with the clinical history and findings Papanicolaou smears of bronchial washings are usually negative for tumor cells. The adenomas are covered in most instances by intact mucosa so that tumor cells are not found in the bronchial washings

Roentgen Appearance

The adenoma may present one of two roentgenographic patterns It may be seen on roentgenograms of the chest as a rounded smooth mass usually at or near the hilum in a patient without symptoms (fig. 5). This was the appearance in two of the 37 cases in this series More commonly, however,



Fig 5—Chest roentgenograms of a 32 year old woman showing a typical rounded hilar shadow caused by an adenoma This patient was asymptomatic The tumor was discovered on a routine survey film Patient alive and well 4 years after a right middle lobectomy

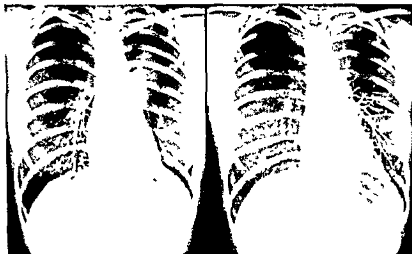


Fig 6—Bronchograms of a 16 year old white girl who had had a cough and wheezing respirations for 18 months A preoperative bronchogram (A) showed an obstruction caused by an adenoma in the left upper lobe A left upper lobectomy with a plastic repair of the bronchus was performed Postoperative bronchogram (B) with the remaining lower lobe expanded to fill the left chest (see figure 7 for diagram of the bronchoplastic repair)

one finds the roentgen appearance associated with obstruction of a bronchus to a lung, lobe or segment with loss of volume or obstructive pneumonitis of the involved portion of lung depending on the degree of mechanics of the obstruction Bronchograms and stratograms may be of great value in demonstrating the nature and site of the bronchial obstruction (fig 6) Out of 37 patients in our series 28 had demonstrable lesions by one or more roentgenographic technics

Treatment

Proper treatment of the bronchial adenoma must be based on an accurate diagnosis as well as a thorough knowledge of the long natural course of the tumor, its tendency to recur locally after inadequate removal, and its malignant potentialities Surgical removal of the tumor is the accepted treatment of choice Endoscopic removal was advocated for many years by some but now has been abandoned except in certain special situations There are several objections to bronchoscopic removal as a method of treatment of bronchial adenomas It has been shown that the portion of the tumor available for removal by bronchoscopy constitutes only a small part of the tumor in most cases, thus explaining the high rate of local recurrence after endoscopic removal Serious and even fatal bleeding following endoscopic removal is not infrequent In the majority of cases the symptoms caused by the ade-

noma are those due to chronic suppurative disease associated with the b chial obstruction. In many instances these symptoms can be alleviated by removal of the chronically infected lung distal to the obstructing noma. Endoscopic removal may still be indicated, however, in seve debilitated elderly individuals who would not tolerate operation but patients constitute a very small percentage of those patients with adenoi Repeated checks for recurrence are necessary if the adenoma is remove bronchoscopy, because local recurrence can occur and has been reporte long as 10 years after endoscopic removal. Because of the slow growth tendency to metastasize late in its course, a limited resection is often quate for complete removal of these tumors. Bronchoplastic procedu which accomplish the complete removal of the tumor and yet preserve lung uninvolved by tumor or chronic infection, have their greatest useful

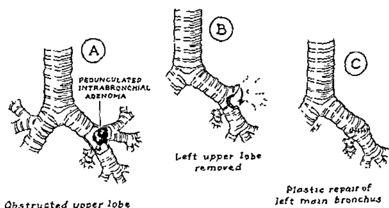


Fig 7—Bronchoplastic procedures done in five cases. These patients are all alive well from one to ten years following operation with no evidence of recurrence Case 1 (*abo*

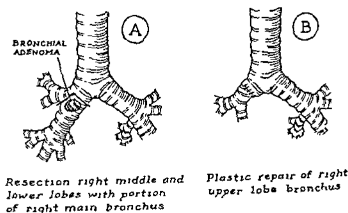


Fig 7—(*continued*) Case 2

in the treatment of this tumor Five of the 37 patients in this series had such procedures with excellent results (fig 7). In most of our cases, however, lobectomy or pneumonectomy was necessary Lobectomy was performed in 11 cases, bilobectomy in 10 and pneumonectomy in six cases

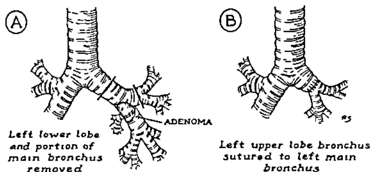


Fig 7—(*continued*) Case 3

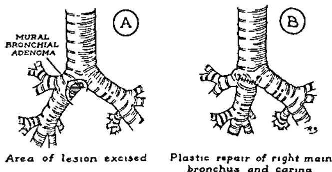


Fig 7—(*continued*) Case 4

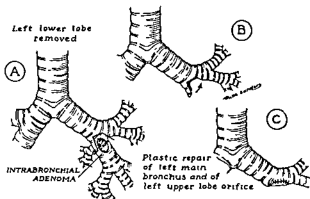


Fig 7—(*continued*) Case 5

Irradiation Therapy

Irradiation therapy may be of value in the cylindromatous adenomas when surgical removal is not possible. We have used irradiation therapy in two cases of recurrent cylindromas of the bronchus and in one extensive cylindroma of the trachea with perhaps some beneficial results. There is very little evidence from reports in the literature that irradiation therapy has any effect on the carcinoid adenoma

Results

The results of the surgical treatment of the adenomas and particularly the carcinoid type have been very gratifying (fig. 9). Out of a group of 21 patients who had either a lobectomy or bilobectomy 19 or 90 per cent are

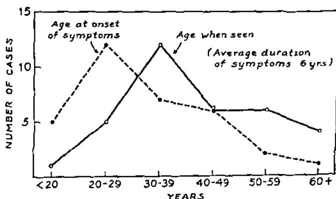


Fig 8—Age of patients at onset of symptoms and age when seen The average duration of symptoms was 6 years

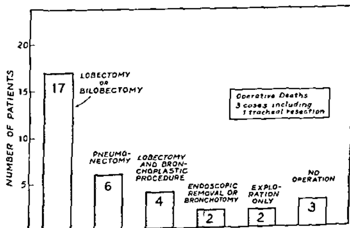


Fig 9—Treatment of 37 cases of bronchial adenoma. Of the 27 patients who had surgical excision of their tumor 23 (84 per cent) are known to be living and well, 2 patients are dead, and 2 have been lost to follow up.

known to be living and well as long as 17 years after operation We have been unable to locate one patient and one died 19 years after her original operation. This patient had a left lower lobectomy for a cylindroma which recurred 12 years later in the bronchial stump A second operation was performed but resection was not possible because of the extensive spread of the tumor to the pericardium, diaphragm and mediastinum This patient lived for seven years after her second operation Six patients had a pneumonectomy performed and of this group three are living and well as long as seven years after operation One of the patients who had a pneumonectomy has been lost to follow up and another died eight years after her original operation This patient was a 39 year old woman who had a cylindroma of the left main bronchus removed by left pneumonectomy. Seven years after operation she was found to have a cylindromatous adenoma in the right upper lobe which was removed by segmental resection This patient died several months after her second operation It is interesting that the only two late deaths in the resection cases have been in patients who had cylindromas

In 3 patients exploration only was done At the time of operation the tumor was found to be too extensive for resection One was in a 34 year old woman who had had repeated illnesses due to lung abscess and empyema requiring drainage on several occasions Pneumonectomy was attempted but was impossible because of extensive involvement of pericardium and pulmonary vessels The patient died a week later of complications of suppurative disease of the lung One of these patients died six years aften exploration with metastases to the abdomen The other patient is still living three years after operation but with roentgen evidence of a large mediastinal mass

No operation was performed in three cases One patient refused operation after a bronchoscopic biopsy and is stilll living without symptoms *16 years later* Another patient who refused to accept surgical treatment died eight years later with metastases to the mediastinum and scalene nodes A third patient was not operated on because of metastases to the spinal canal This patient was a 65 year old paraplegic with severe heart disease who for 30 years had had complete opacity of her left lung field on roentgen examination This was caused by obstruction of her bronchus by an adenoma which could be seen at the time of bronchoscopy

One patient in this series had a bronchoscopic removal of a small polypoid adenoma This patient is alive and free of evidence of recurrence seven years after removal Another patient had a very limited resection of an adenoma and a plastic repair of the defect without removal of any lung tissue (fig 7). This patient is alive and free of recurrence eight years after operation.

Bronchoplastic procedures have been performed in five patients (fig 7). All of these cases have done well and have shown no evidence of recurrence in the period since operation which in one case has been as long as ten years

Limited resection has been used wherever possible in order to preserve all lung tissue not involved by tumor or chronic infection. Goldman has recommended consideration of local excision in every case where the following conditions can be met.

The tumor—

1 is established to be benign, semibenign or only potentially malignant
2 has not undergone malignant degeneration, metastasized, or widely infiltrated the bronchus
3 is located in the trachea or an easily accessible bronchus
4 is localized, has no extensive extrabronchial growth and has not caused pressure necrosis
5 has a stalklike or small area of sessile attachment
6 has caused no irreversible pulmonary damage in the lung distal to its location

Complete excision of the trachea was performed in one patient who had a cylindroma involving most of his thoracic trachea and extending downward to involve both the right and left main brouchi. This patient was threatened with suffocation from complete tracheal obstruction. Irradiation therapy had been tried but the obstruction became worse necessitating abandonment of this form of therapy. Approximately 12 cm. of the trachea and coryna and bifurcation were resected and replaced with a prosthesis fashioned of dermis over a coil of steel wire. This patient died two days following operation from respiratory obstruction due to kinking of the major bronchi at the site of the anastomoses In two similar cases with one survival reported by Belsey in neither case was resection of the entire tracheal circumference necessary. Both of these cases had cylindromas resected and the tracheal defect repaired with a prosthesis made of fascia from the patient's thigh and no. 32 guage stainless steel wire.

Operative Deaths and Complications

There were three operative deaths One occurred following exploration mentioned above. The second occurred in a 32 year old woman who expired on the operating table due to inadequate ventilation. It was discovered too late that the endotracheal tube had slipped down into the right main bronchus The third death occurred following resection of the trachea for a cylindroma, already referred to above.

Postoperative complications occurred in seven patients. Two patients had postoperative hemorrhage necessitating reopening of the chest to control the bleeding One patient developed a superficial hematoma of the wound which caused a disruption requiring secondary closure. Two patients developed an empyema following a small bronchial leak. These cases were successfully treated by closed thoracotomy and tube draining. In one case there was roentgen evidence of infarction of the right lower lobe pre-

sumably due to damage to the blood supply at the time of operation This cleared without treatment.

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CHAPTER 11

Miscellaneous Tracheobronchial Tumors

By PAUL H HOLINGER, M D.

INFLAMMATORY TISSUE MASSES, amyloid deposits and benign and malignant neoplastic growths constitute a significant group of miscellaneous tracheobronchial tumors Each is a relatively rare pathologic entity but their clinical characteristics are sufficiently similar that differentiation is dependent on the histologic evaluation These tumors give evidence of their presence in the trachea or bronchi by symptoms of cough and hemoptysis, as well as by those symptoms and findings associated with partial or total airway obstruction such as wheezing and dyspnea, obstructive emphysema and atelectasis Cough is generally the first symptom Wheezing is often intermittent, present as the patient lies in certain positions or changes his position Dyspnea is primarily due to tracheal or bronchial obstruction, but may also be caused by mediastinal or vascular compression Hemoptysis is rarely an early symptom of patients with benign tumors Pulmonary suppuration is usually the cause of hemoptysis when it does occur, and is responsible for most of the systemic symptoms of bronchial tumors Partial or complete obstruction of the bronchus results in impaired drainage which predisposes to infection in the related lung, often giving the signs and symptoms of a clinical pneumonia This has a segmental or lobar distribution depending on the bronchus involved, and responds readily to chemotherapy to give temporary, symptomatic relief Subsequent x-rays show incomplete resolution as the acute process is followed by chronic suppuration Further study of such a patient for signs of bronchial obstruction are essential if the early diagnosis of a bronchial tumor is to be made The development of a lung abscess or bronchiectasis with a constant productive cough sometimes associated with hemoptysis is typical of a chronic obstruction due to a bronchial neoplasm The abscess may result from a necrotic slough of the tumor or from a necrotizing pneumonia behind the bronchial obstruction Chest pain or a feeling of constriction of the chest is a symptom seen most constantly in bronchogenic carcinoma, although chest pain may be associated with a benign tumor In rare instances the arthritic symptoms of pulmonary osteoarthropathy are seen in benign bronchopulmonary tumors, the degree of symptoms being in no way relative to the size of the tumor Removal of the tumor results in a dramatic relief of the arthritic symptoms, often within a few hours

Many benign tumors are symptomless or "silent," detected on routine

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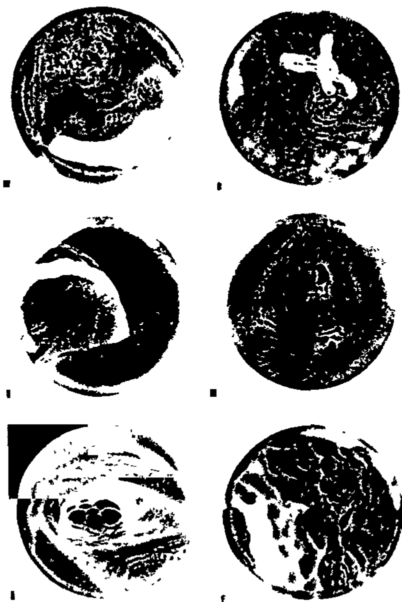


Fig 1—Bronchoscopic photographs of endobronchial tumors (A) A granuloma obstructing the right main bronchus The tumor was found at the site of repair of a fracture of the bronchus incurred in an automobile accident (B) Sutures seen within the bronchus following removal of the granuloma (C) Inspiration, and (D) expiration photographs of a tuberculous granuloma in the right lower lobe bronchus This check-valve phenomena resulted in an obstructive emphysema distal to the tumor (E) Papilloma on the floor of the right lower lobe bronchus The middle lobe orifice is seen anteriorly, the orifice of the superior division of the lower lobe is just proximal to the tumor (F) The lateral wall of the trachea showing the bony spicules of tracheopathia osteoplastica

chest surveys or reported as incidental post-mortem observations The apparent increased incidence of such lesions recorded in the recent literature is due to recognition of the potential danger of malignancy in asymptomatic x-ray shadows in the lung. Bronchoscopic or surgical exploration shows many of these silent lesions to be benign, but such a high percentage are malignant that bronchoscopic and surgical investigation of all is indicated

There are two aspects to the pathology of the miscellaneous tracheobronchial tumors; the histology of the tumor itself and the effect of the tumor on the lung distal to the tumor.

Inflammatory Tumors

The inflammatory tumors constitute a relatively large group of tumors found in the lower respiratory tract The simplest are the polyps and the nonspecific granulomas. The polyps are often associated with other evidence of allergic disease while the nonspecific granulomas are usually secondary to endogenous or exogenous foreign bodies The specific granulomas are extremely varied in their pathology and are almost always intrabronchial manifestations of a systemic disease.

Endobronchial polyps are relatively uncommon The etiology is somewhat obscure, although chronic bronchopulmonary suppuration and asthmatic bronchitis are often present in patients found to have endobronchial polyposis The histology is similar to that of nasal polyps, consisting of edematous folds of mucosa with a respiratory type of epithelium. There is a loose fibrovascular myxomatous stroma containing blood vessels and a few lymphocytes The polyps are more often single than multiple and if pedunculated may cause a variable clinical picture with a shifting atelectasis depending on the branch bronchus they obstruct. Diagnosis is considered in any patient with bronchial obstruction, but confirmed only on histologic examination of a bronchoscopically obtained biopsy. Therapy consists of bronchoscopic removal by forceps, bronchoscopic snare or coagulation, although if lung destruction distal to the polyp is irreversible, resection of the segment or lobe would be indicated. Under these circumstances, the polyps may be included in the resected tissue, but prior endoscopic removal may facilitate drainage, thus improving the postoperative course.

Nonspecific granulomas are common endobronchial tumors. They may surround and conceal broncholiths or aspirated foreign bodies, often occluding a bronchus in a week or ten days after a foreign body aspiration They may develop in the suture line of a resected bronchus or at the points of closure of a tracheotomy or a bronchotomy. The bronchoscopic removal of a granuloma from the region of a bronchotomy closure usually discloses the presence of one or more of the sutures that had been used in the repair process The suture should be removed with forceps to permit healing The healing of a bronchus fractured by external trauma may be complicated by



Fig 1—Bronchoscopic photographs of endobronchial tumors (A) A granuloma obstructing the right main bronchus The tumor was found at the site of repair of a fracture of the bronchus incurred in an automobile accident (B) Sutures seen within the bronchus following removal of the granuloma (C) Inspiration, and (D) expiration photographs of a tuberculous granuloma in the right lower lobe bronchus This check-valve phenomena resulted in an obstructive emphysema distal to the tumor (E) Papilloma on the floor of the right lower lobe bronchus The middle lobe orifice is seen anteriorly the orifice of the superior division of the lower lobe is just proximal to the tumor (F) The lateral wall of the trachea showing the bony spicules of tracheopathia osteoplastica

the formation of granulomas necessitating frequent endoscopic removal to maintain a normal airway (fig 1A and B). Nonspecific granulomas contribute to the chronicity of a lung abscess by obstructing the lobar or segmental bronchus leading to the abscess. Removal of such granulomas facilitates endobronchial drainage and is an important aspect of the therapy of lung abscess.

Specific Granulomas. Tuberculomas are the commonest of the specific inflammatory tumors. These may follow the organization of granulation tissues associated with the rupture of a hilar node into a bronchus. They also occur during the cycle of healing of an ulcerative tuberculous process of the bronchial wall. In either case, partial or total bronchial obstruction may follow, with the findings of obstructive emphysema or atelectasis depending on the degree of bronchial obstruction Figure 1C and D shows a tuberculoma of the right lower lobe bronchus during the two phases of respiration, demonstrating the mechanics of the check-valve phenomena Figure 2 shows an atelectasis shown on bronchoscopy to have been caused by total bronchial obstruction due to a tuberculous granuloma, probably tissue from a ruptured hilar node. Solitary tuberculomas may be found in the bronchus of adults or children whose histories, x-rays and bronchoscopic findings suggest an adenoma or bronchogenic carcinoma. Sputum is not necessarily positive, the final diagnosis being apparent only on histologic examination of the resected tumor

Intrabronchial tumors due to Boeck's sarcoid have likewise been described These masses have no characteristic endoscopic appearance but histologic diagnosis may be made from biopsy specimens Severe bronchial obstruction is relieved by forceps removal of tissue and systemic cortisone therapy

A rare specific inflammatory tumor of the bronchus is a syphilitic granuloma A positive serology and histologic examination of resected tissue confirms the diagnosis. Total bronchoscopic removal of obstructing tissue and adequate antiluetic therapy are indicated

Other specific inflammatory tumors of the bronchus are those of rhinoscleroma, and torula, actinomycosis, blastomycosis and other fungus infections The bronchial tumors caused by rhinoscleroma are commonly seen in patients from Central Europe, Mexico and Central America These tumors are firm, nodular and usually are continuations of the process in the larynx and upper respiratory tract The gross pathologic appearance consists of rounded, irregular thickenings of the walls of the trachea and bronchi with more discrete tumors superimposed on an ulcerated, roughened surface. The nodular thickening of the walls of the airway frequently causes death by asphyxia since the process descends into the bronchi where obstruction cannot be relieved by a tracheotomy.

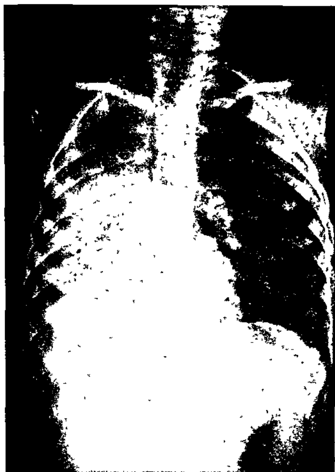


Fig 2—Atelectasis of the right middle and lower lobes due to total obstruction of the bronchus by a tuberculous granuloma Multiple areas of lung destruction are seen in the atelectatic area

Both torula and actinomycosis may produce intrabronchial tumors in association with a bronchopulmonary suppurative process The diagnosis is established by histologic examination of bronchoscopic biopsies and careful prolonged culture studies of aspirated secretions Tissue cultures for fungus forms, and establishment of pathogenicity through animal transfer are essential criteria of diagnosis Endobronchial resection provides drainage although resection of affected pulmonary tissue distal to the obstruction may be necessary Extensive atelectasis, bronchiectasis and lung abscess often complicates and obscures the true underlying disease process

Amyloid Pseudotumors of the Trachea and Bronchi

Amyloid tissue masses are not true tumors. However, deposits of the mucopolysaccharide-protein complex which constitutes the amyloid masses give the gross appearance and the mechanical effects of tumorous obstruction of the airway and, therefore, are described here. A distinction must be made between those cases in which the amyloid deposits are part of a generalized amyloidosis and those in which the deposition of amyloid is localized with no evidence of a generalized amyloid disease. The localized amyloid deposits in the trachea and bronchi can be divided into three groups degeneration of a previous tumor, isolated tumor-like formation, and a diffuse subepithelial infiltration

Amyloid tumors of the tracheobronchial tree are rare. The recognition of primary amyloid disease in the respiratory system may follow investigation of hoarseness, or signs of respiratory obstruction, and the diagnosis is made on microscopic examination of tissue removed by endoscopic biopsy Most of the cases occur after the fifth decade of life, and are more frequent in males than in females in the ratio of three to one The symptomatology is not characteristic. The type and degree of symptoms will depend on the location and site of the mass; in some instances, the tumor is an incidental finding at autopsy

Grossly, amyloid tumors are granular in appearance and are yellowish or red-tinged in color. They have a waxy translucent surface without ulceration. In those instances in which Congo red has been injected intravenously prior to visual examination the material can be seen to have taken on a corresponding red coloration. The limitations of the tumor can thus be more easily determined The systemic Congo red absorption is usually unaltered in primary localized amyloidosis since the amount of amyloid tissue in these instances is comparatively small as compared with secondary amyloidosis. A positive diagnosis of amyloid tumor is made on the microscopic examination of tissues which have been sectioned and stained in the routine manner with hematoxylin and eosin A regular mucosal surface encompasses rounded masses of varying sizes composed of hyaline material, in the interstices of which lymphocytes and plasma cells may be present. There may be a subepithelial infiltration of a homogeneous hyaline substance forming concentric layers with giant cell infiltration. An involvement of the capillaries with this type of infiltration has been described as well as involvement of the mucous glands with replacement of the glands by amyloid masses.

The most satisfactory treatment is surgical removal of the amyloid deposits. In most instances endoscopic removal is adequate, particularly when the tumor is localized to a small area If the lesion is diffuse, endoscopic removal should be done, taking as much of the tissue as can be obtained with forceps, snare or resectoscope If large areas of disease have to be excised,

the cut surfaces may have to be covered with a skin graft. Surgical removal is not as a rule followed by recurrence, although recurrence after partial removal is possible. No instances of malignant change in amyloid tumors of the trachea and bronchi have been reported The prognosis is, therefore, entirely dependent on the situation and extent of the mass Due to the fact that the tumor is in the airway, the degree of respiratory obstruction determines the prognosis

Benign Neoplastic Tumors

Liebow classifies neoplastic tumors of the bronchi as epithelial, mesodermal and tumors of developmental origin Papilloma and papillomatosis of the bronchial tree is the only benign epithelial tumor considered Benign mesodermal tumors consist of fibromas, lipomas, fibrolipomas, chondromas, osteochondromas and granular cell myblastoma Hemartomas are listed separately as tumors of developmental origin Fibromas, fibrolipomas and lipomas appear to be the most common benign tumors of the trachea and bronchi and the papilloma next in order of incidence

A *fibroma* of the bronchus is a slow-growing tumor that usually becomes apparent through symptoms of bronchial obstruction, with wheezing, cough, dyspnea, recurring pneumonia and atelectasis A persistence of atelectasis results in lung destruction and bronchiectasis with this secondary pathology far outweighing the seriousness of the pathology of the tumor itself Bronchoscopically, the tumor is seen as a smooth, round, firm, pink mass, sometimes nodular and usually pedunculated Purulent material from beyond the tumor often prevents an accurate bronchoscopic evaluation on the first examination, and repeated bronchoscopic aspirations may be required before a satisfactory biopsy can be obtained Histologically, the tumor consists of closely packed spindle-shaped cells, some containing considerable fatty tissue These may be designated as fibrolipomas, differentiated from the fibromas themselves only on histologic evidence

The therapy is determined by many factors Pedunculated fibromas may be removed by bronchoscopic forceps or snares Accurate application of the snare and very slow closure of the snare wire around the base serves to reduce the possibility of hemorrhage The use of a bronchoscopic resectoscope and a combined cutting and coagulating current also provides an excellent bronchoscopic means of removing the tumor External surgery is indicated if the lesion has a long sessible base, when excision of the tumor through a bronchotomy is more feasible In cases of long duration, when persistent atelectasis has been followed by extensive bronchiectasis, or if there is x-ray evidence of extrabronchial extension of the tumor, surgical excision of the entire diseased area, by lobectomy or pneumonectomy, is indicated

Intrabronchial lipomas are relatively uncommon, benign fatty tumors

usually seen in the major bronchi They are *more often seen in men than in* women, and usually in the fifth and sixth decades. They produce respiratory obstruction and the pulmonary changes secondary to long-standing bronchial obstruction The history is that of recurring wheezing and pneumonia with severe coughing spasms unaccompanied by hemoptysis The tumor is soft, smooth, pale in color, often pedunculated and generally does not extend beyond the cartilagenous bronchial walls The diagnosis is established bronchoscopically, as the round, smooth mass is seen obstructing the bronchial lumen *Bleeding on removal of tissue for biopsy is not active as it* would be in an adenoma, a tumor with which it might readily be confused, grossly Histologically, the lipoma consists of lobules of mature fat cells between which is interlaced a delicate fibrous stroma. Lipomas apparently arise from adipose tissue normally present in the submucosa Treatment is usually endoscopic since those tumors of clinical significance are in the major bronchi. A bronchoscopic snare may be used, with or without surgical diathermy, or simple forceps removal may suffice. If an upper lobe bronchus is *involved, an artificial pneumothorax brings this bronchus into direct* alignment with the bronchoscope If lung destruction beyond the tumor has occurred, lobectomy or pneumonectomy may be indicated.

Papilloma of the trachea or bronchus is most frequently seen in infants and children as an extension of this tumor from the larynx The descent of laryngeal papillomata into the subglottic area is common, but, advancement of the process to involve the trachea or bronchi is, fortunately, less frequently seen Isolated primary tracheal or bronchial papillomas are rare *and are seen most often in adults (fig. 1E).*

Histologically the papilloma consists of stalks of connective tissue on which layers of stratified squamous epithelium are seen in deep folds. Many branches and folds repeat the structure, each with a central *connective tissue* stalk. Extension of the papilloma from the larynx to the trachea or bronchi appears to be due to aspiration implants. The condition may be severe around the tracheal bifurcation and in occasional cases the lesions progress to the bronchi, bronchioles and into open cavities throughout the lungs. The diagnosis of tracheal and bronchial papillomatosis is *obvious when the* warty, cauliflowerlike growths are seen as an extension of a similar laryngeal process. In the child tracheotomized for laryngeal papilloma, continued *distress with wheezing, obstructive emphysema* and atelectasis indicate such partial or complete lower respiratory tract involvement. The diagnosis is [illegible] will

of repeated bronchoscopic removals of the masses as they [illegible] sion may ultimately cause asphyxia as the trachea and both bronchi become obstructed by the tumors or by scar tissue. Resection of *the trachea has* been reported.

Chondromas and osteochondromas are cartilagenous and bony tumors occasionally seen in the trachea and major bronchi They generally appear as enlargements of existing tracheal or bronchial cartilages, but may be completely separated from normal cartilagenous rings, surrounded by their own capsule They are firm and when ossified may be glass-hard making accurate bronchoscopic biopsy almost impossible They are very slow growing and, therefore, are associated with extensive bronchopulmonary destruction since they sometimes attain a relatively large size, both within and outside of the bronchus They may cause asphyxia by obstruction of the trachea or a major bronchus The serious potential danger is the degeneration into a malignant sarcomatous form

The differentiation between a chondroma and a hamartoma is made histologically, the chondroma containing only cartilagenous tissue covered by mucosa When intrabronchial and pedunculated, this tumor may be removed by bronchoscopic snare Bronchotomy is necessary if the base is sessile When the tumor is dumbell in shape or has caused bronchiectatic changes in the periphery, resection of the affected segments or lobes is indicated

Hamartomas are bronchial tumors of developmental origin and are often classified with chondromas They contain cartilage, sometimes ossified connective tissue, fat cells, smooth muscle fibers, bundles of epithelial cells and often a connective tissue capsule Although bronchial elements other than cartilage are present, they cannot be considered teratomas because only bronchial elements are found and hamartomas contain no tissue other than those of bronchopulmonary origin They are generally seen in the periphery of the lung as solitary, hard masses, less than 1 cm in size, most often as incidental findings on x-ray or post-mortem examination They are rarely seen in children and are more common in men than in women in a ratio of two or three to one Hamartomas are most often "silent lesions" and are entirely symptomless, Occasionally, however, they are found as large, round, or lobulated hard masses up to 9 cm in size When they compress or invade the tracheobronchial tree the obstruction produces the associated bronchopulmonary symptoms of cough, wheezing, dyspnea and chest pain In their clinical aspects they simulate chondromas and only careful histologic examination indicates the true nature of the tumor Rare cases have been reported in which the tumor is entirely intrabronchial Occasionally, hamartomas are multiple or widespread and involve an entire lobe or lung. Therapy consists of conservative surgical resection In the rare instance in which the tumor is intrabronchial, resection can be accomplished bronchoscopically, and in some cases, the diagnosis has been established by bronchoscopic biopsy of an intrabronchial extension of the tumor

Tracheopathia osteoplastica is a rare condition of the tracheal and bronchial cartilages consisting of multiple small, bony-hard projections into the tracheal lumen The projecting masses are mucosa-covered and involve only

usually seen in the major bronchi. They are more often seen in men than in women, and usually in the fifth and sixth decades They produce respiratory obstruction and the pulmonary changes secondary to long-standing bronchial obstruction. The history is that of recurring wheezing and pneumonia with severe coughing spasms unaccompanied by hemoptysis The tumor is soft, smooth, pale in color, often pedunculated and generally does not extend beyond the cartilagenous bronchial walls. The diagnosis is established bronchoscopically, as the round, smooth mass is seen obstructing the bronchial lumen Bleeding on removal of tissue for biopsy is not active as it would be in an adenoma, a tumor with which it might readily be confused, grossly Histologically, the lipoma consists of lobules of mature fat cells between which is interlaced a delicate fibrous stroma Lipomas apparently arise from adipose tissue normally present in the submucosa. Treatment is usually endoscopic since those tumors of clinical significance are in the major bronchi. A bronchoscopic snare may be used, with or without surgical diathermy, or simple forceps removal may suffice. If an upper lobe bronchus is involved, an artificial pneumothorax brings this bronchus into direct alignment with the bronchoscope. If lung destruction beyond the tumor has occurred, lobectomy or pneumonectomy may be indicated.

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strate the characteristic bony spicules X-rays show the irregular, bony tracheal walls and planograms (fig 3) clarify the diagnosis The bronchoscopic picture is most startling (fig 1F) The tracheal surfaces except for the posterior wall consist of a mass of irregular, hard, mucosa-covered projections that cannot be removed by any of the commonly used biopsy forceps The walls are hard and thick and encroachment on the lumen may be severe enough to embarrass respiration Serum calcium studies show no abnormal calcium metabolism, and x-rays of all body structures show no unusual calcium deposits elsewhere There is no known therapy other than supportive measures designed to improve bronchial drainage Expectorants and the use of antibiotics if obstruction has caused a pneumonitis are indicated When dyspnea is severe, the forcing of a bronchoscope through the obstructed tracheal lumen is virtually the only therapy of any assistance Mechanically fracturing and removing those masses causing the greatest obstruction is accomplished by this procedure

Hemangiomas involving the trachea are seen in infants generally as part of an extensive or multiple hemangiomatous process that involves the face and the buccal mucosa The elevation of the soft, dark red tissue is apparent on the laryngeal and tracheal mucosa and it may cause severe stridor and respiratory obstruction The lesion is most commonly seen in the subglottic area, and tracheotomy of a newborn may be necessary because of the obstruction Irradiation in this area should be administered with great caution because dosage adequate to destroy the tumor may likewise destroy the potential growth of the larynx, resulting in severe chronic laryngeal stenosis

Myomas Benign muscle tumors within the bronchus are exceedingly rare, but have been encountered on bronchoscopic examination made to determine the etiology of a bronchial obstruction Other myomas have been detected when a routine survey chest film has revealed a "silent lesion" and the subsequent bronchoscopic or external surgical exploration has demonstrated the nature of the tumor. Endoscopic resection is effective if the tumor is entirely endobronchial, but if planograms or heavy density films show extrabronchial tumor density, segmental resection or lobectomy is indicated

Malignant Neoplastic Tumors (Other than Bronchogenic Carcinoma)

Tumors of a malignant character other than bronchogenic carcinoma constitute a relatively large group of miscellaneous tracheobronchial tumors Those that are primary in the trachea and bronchi are the sarcomas, the malignant counterparts of the benign tumors described, fibrosarcoma, myosarcoma, etc. Others, such as lymphosarcoma and Hodgkin's Disease are intrabronchial manifestations of systemic tumors. A third group consists of intrabronchial metastatic tumors which apparently have been seeded

the lateral and anterior walls since they originate from the cartilagenous rings. Their etiology is obscure although it has been suggested that they are the result of the deposition of multiple anomalous anlage of cartilagenous tissue in the tracheal mucosa.

Clinically, this lesion may be an incidental finding on x-ray or at postmortem study. Occasionally, symptoms of wheezing, cough, hemoptysis and gradually increasing dyspnea lead to bronchoscopic studies which demon-



Fig 3—Planogram of the trachea of a patient with tracheopathia osteoplastica The calcified irregularities and the tracheal stenosis are seen.

CHAPTER 12

Mediastinal Tumors

By HAROLD A LYONS, M D.

AN EXTRAORDINARY VARIETY OF IMPORTANT STRUCTURES lie in the mediastinum the heart itself, the great arteries and veins, the principal lymph channels and their many lymph nodes, segmental sympathetic and parasympathetic nerves, air passages (the trachea and main bronchi), the esophagus, glands of internal secretion (the thymus and often the thyroid and parathyroids) Any one of these diverse tissues may give rise to a pathologic mediastinal mass

The mediastinum is also an area for faulty embryogenesis It is in this area that the bronchial arteries unite, that the pulmonary buds arise, which in their turn branch and subdivide into the bronchial tree, the foregut differentiates, and the tubular heart undergoes its rotation and divisions Here, too, the pleural and pericardial sacs are formed, and the formation of the diaphragm occurs These formations, when faulty, may lead to cysts, or solid tumors of aberrant tissue

Because the mediastinum is a rich and central area for lymphatic drainage, it is frequently the site of lesions originating elsewhere, for example, (1) direct invading bronchogenic carcinomas, (2) metastases from carcinoma of the lungs or the abdominal organs, (3) inflammatory diseases, especially granulomas, or (4) the generalized disorders such as lymphoblastomas Defects of the diaphragm or its openings may have protrusions of intestinal organs or omentum located in the mediastinum Effusions or empyemas, may be present within the mediastinum or intimately connected with it Vertebral disease and scoliosis distort the mediastinum Occasionally, a herniation of the lung across the mediastinum may give the impression of a mediastinal cyst Malformations and aneurysms of the great vessels may pr [illegible]

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The increasing utilization of chest roentgenography as a result of mass x-ray surveys for the discovery of pulmonary tuberculosis, routine admission chest films in hospitals preinduction and annual physical examination chest

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Because the mediastinum is a rich and central area for lymphatic drainage, it is frequently the site of lesions originating elsewhere, for example, (1) direct invading bronchogenic carcinomas, (2) metastases from carcinoma of the lungs or the abdominal organs, (3) inflammatory diseases, especially granulomas, or (4) the generalized disorders such as lymphoblastomas Defects of the diaphragm or its openings may have protrusions of intestinal organs or omentum located in the mediastinum Effusions, or empyemas, may be present within the mediastinum or intimately connected with it Vertebral disease and scoliosis distort the mediastinum Occasionally, a herniation of the lung across the mediastinum may give the impression of a mediastinal cyst Malformations and aneurysms of the great vessels may produce mediastinal masses which may be thought to be a tumor

Abnormal masses of the type described above can no longer be considered rare or even uncommon An almost endless variety of lesions have been encountered in the mediastinum Their differential diagnosis embraces virtually every endothoracic disorder An accurate history and complete physical examination are necessary

The increasing utilization of chest roentgenography as a result of mass x-ray surveys for the discovery of pulmonary tuberculosis, routine admission chest films in hospitals, preinduction and annual physical examination chest

roentgenograms by the military services, the pre-employment films in industry, and the widespread policy of making a chest x-ray study a part of the study of any patient, has increased greatly the number of mediastinal lesions seen by physicians.

The discovery of a mass believed to be in the mediastinum immediately raises several questions. Is it within the pulmonary parenchyma, or in the pleural space? Is it probable that the mass represents a benign tumor or a malignancy? Is the lesion one amenable to surgery, other therapy, or neither? To answer these queries requires other investigations, a good lateral film, and, if necessary, oblique roentgenograms are needed The position of a tumor in the mediastinum is the best guide to its identity (fig 1) Radiologic screening is indispensable for the mobility, change in size with respiration and pulsations. Confirmatory evidence of serologic tests and characteristic physical signs are needed for further information. Kymography for *pulsations, tomography and angiocardiography are important studies for* position, for involvement and the degree of the involvement of proximal structures. Barium swallows should never be omitted lest esophageal lesions, diaphragmatic hernias or pressure effects on the esophagus be unknown. Bronchoscopy is an essential diagnostic procedure (see table 1).

An orderly investigation of mediastinal masses employing those examinations which appear to be indicated will enable one to verify the mediastinal position of the mass in almost every case, and it will usually give sufficient information for the proper management of the individual patient. Two diagnostic procedures, (1) the scalene node biopsy, and (2) angiocardiography, are most helpful Scalene node biopsy yields a significantly high percentage

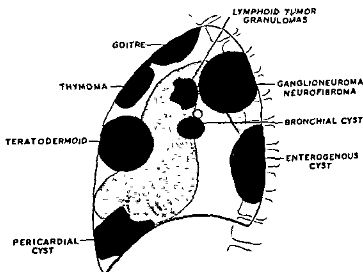


TABLE 1—*Diagnostic Procedures*

Roentgenographic Studies	Surgical Procedures	Miscellaneous
1 Posterior anterior stereoscopic and lateral chest roentgenograms	1 Bronchoscopy	1 Skin tests for specific granulomas
2 Fluoroscopy*	2 Scalene node biopsy†	2 Sputum studies for organisms and malignant cells*
3 Potter-Bucky grid films	3 Biopsy Abnormal nodes Liver Pleura Other tissues	3 Tracer dose of radioactive iodine
4 Supervoltage roentgenograms	4 Thoracotomy†	4 Slit lamp examination for sarcoid granuloma
5 Tomograms	5 Thoracentesis	5 Bone marrow studies
6 Esophagrams		
7 Kymograms		
8 Angiocardiograms†		
9 Retrograde angiograms		
10 Barium visualization of gastrointestinal tract		
11 Bronchograms		
12 Myelograms		
13 Diagnostic pneumothorax and pneumoperitoneum		

* This diagnostic study is most valuable and may often detect a tumor vaguely seen by other methods It will also show characteristic helpful signs

† The most definitive and valuable special procedures, often precluding further examination

of positive diagnosis to warrant its routine use Its greatest value has been in lymphomas, certain granulomas, and mediastinal or pulmonary tumors Angiocardiography has reduced the number of instances in which thoracotomy would be necessary for the diagnosis of a noncorrectible vascular lesion Aneurysms, coarctation and cardiac abnormalities resembling mediastinal neoplasms have been differentiated by the procedure It has also aided in clearly defining the relations of tumors to the adjacent cardiovascular structures In this manner, an estimate of operability of a given tumor, and plan for the surgical approach can be made It is safe to state that one of the most decisive factors in the successful extirpation of a mediastinal tumor is its separation from the large vessels or parts of the heart with which it may be in intimate contact, it is here that angiocardiography provides a safeguard for the operation

If the diagnostic studies fail to establish a specific diagnosis, exploratory thoracotomy should be undertaken *Procrastination does not serve the best interests of the patient*

The clinical manifestations and radiologic appearance can give an accurate diagnosis in at least 80 per cent of the mediastinal lesions The location, definition in size shape and relative density of the roentgenographic shadow, the presence of air bone and calcification are of great diagnostic significance Destruction of bone implies malignancy However, benign tumors of nervous origin and aneurysms may show compression erosion of bone.

TABLE 2—*Location of Tumors and Cysts in the Mediastinum**

Anterior Mediastinum	Posterior Mediastinum	Superior Mediastinum	Middle Mediastinum
Thymoma	Neurilemmoma	Goiter	Bronchogenic cyst
Teratoma	Neurofibroma	Bronchogenic cyst	Lymphomas
Goiter	Ganglioneuroma	Parathyroid adenoma	Pericardial cyst
Parathyroid adenoma	Sympathicoblastoma	Myxoma	Plasma cell myeloma
Lymphomas	Fibrosarcoma	Lymphomas	
Lipomas	Lymphomas		
Fibroma	Goiter		
Lymphangioma	Xanthofibroma		
Hemangioma	Gastroenteric cyst		
Chondroma	Chondroma		
Thymic cyst	Myxoma		
Rhabdomyosarcoma	Meningocele		
	Paraganglioma		

* Schlumberger, H G Tumors of the Mediastinum, Atlas of Tumor Pathology, Sect V Fasciale 18 Washington, D C, Armed Forces Institute of Pathology, 1951

Published reports do not show the true frequency of a given tumor encountered at operation or autopsy, but the relative incidence and location of tumors and cysts of the mediastinum are given in figure 1 and Tables 2 and 3. Table 2 lists the location and order of occurrence of mediastinal tumors encountered by Schlumberg at the Armed Forces Institute of Pathology Table 3 shows the incidence of mediastinal tumors encountered by the author listed according to basic type.

TABLE 3—*Incidence of Mediastinal Tumors Grouped Under Basic Types**

Basic Type	No of Cases	Total No of Each Type
CYSTS		
Thymic	12	
Bronchogenic	2	
Gastroenterogeneous	2	
Pericardial	2	
Lymphangitic	1	19
HERNIAS, DIVERTICULA, ACHALASIAS		
Hernias		
Hiatus (esophageal-gastric)	16	
Morgagni	4	
Traumatic	3	
Bochadalek	1	
Diverticula		
Traction	4	
Pharyngeal-esophageal	4	
Achalasias	10	42

TABLE 3—*Continued*

Basic Type	No of Cases	Total No of Each Type
VASCULAR		
Aneurysms		
Great vessels	26	
Innominate artery	3	
Pulmonary artery	2	
Cardiac	5	36
Anomalies		
Dilated tortuous subclavian artery	20	
Coarctation of aorta	5	
Tortuous aorta	3	
Right sided aortic arch	2	
(broncho-pericardial vessel) varices	1	
Great vessels (di Guglielmo type)	1	32
Neoplasms		
Cardiac metastases	14	
Hemangioma—Left ventricle	1	15
NEOPLASM		
Malignant Lymphoma		
Hodgkins	146	
Lymphocytoma	40	
Reticulum cell sarcoma	8	
Lymphatic leukemia	5	
Follicular lymphoma	4	203
Teratoma and dermoid	35	
Thymoma	26	
Neurogenic	15	
"Bronchogenic" carcinoma	8	
Mesenchymal	5	
Metastatic	34	123
INFLAMMATION		
Boeck's sarcoid	160	
Histoplasmosis	53	
Tuberculoma	48	
Coccidioidomycosis	7	
Infectious mononucleosis	7	
Lymph node hyperplasia	3	278
MISCELLANEOUS		
Goiter	20	
Traumatic hematoma	5	
Mediastinitis	3	
Mediastinal effusion	3	
Grand Total		779

* Lyons, H A , Calvy, G , and Salmon, W Mediastinal masses Ann Int Med (in publication)

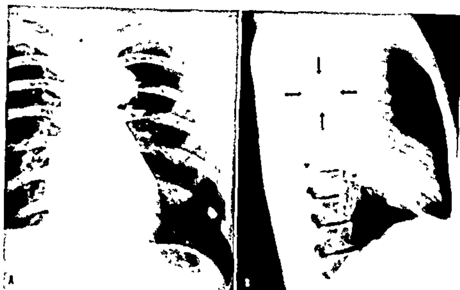


Fig 2—(A) The frontal chest roentgenogram of a 38 year old white male who had no symptoms, but showed this rounded mass in the aortic knob area on an annual physical x-ray examination (B) The lateral chest radiogram shows it located in the posterior mediastinum On surgical removal this was a neurofibroma It has the characteristic of a neurogenic tumor, dense in nature, sharp and round and in the posterior mediastinum

Lymphomas

These tumors are described in detail in Chapter 13 Lymphomas are however the most frequent neoplasms of the mediastinum, and enter into the differential diagnosis frequently

Neurogenic Tumors

For an abnormal mediastinal mass to suggest a neurogenic tumor requires that it be located in the posterior mediastinum, be a dense shadow, sharp and round in character (fig 2A and B).

When a ganglioneuroma is present in the vertebral groove, it may present a spindle-shaped density on the roentgenogram of the chest. Rarely, neurogenic tumors may become so large as to present in the superior or posterior, middle and anterior mediastinum (fig. 3A and B). When they give this radiologic appearance, they simulate thyroid or bronchogenic cysts Large-sized tumors may suggest bronchogenic carcinoma, especially in the older patient Like other mediastinal masses, neurogenic tumors may be located behind the heart and appear indistinctly on routine chest films.

The neurogenic tumors are *the most frequent neoplasms of the mediastinum*, if lymphomas are excluded. They are classified as: neurilemmoma (the most common), neurofibroma, ganglioneuroma, sympathicoblastoma, paraganglioma, pheochromocytoma and malignant schwanoma. The neurilem-



Fig 3—Another example of a neurofibroma is seen in this chest roentgenogram (A) This however on the lateral film (B) was found in the middle mediastinum Biopsy of a skin nodule showed a peripheral neurofibroma On removal this mediastinal mass was found to be a neurofibroma of the right vagus nerve

moma takes origin in the sheath of the nerve These tumors are usually well encapsulated and spherical They are loosely attached to the adventitia of the aorta, but are firmly adherent to the paravertebral tissues At times, such tumors may arise from nerve roots within the spinal canal, grow through the intervertebral foramina and continue to increase in size within the mediastinum Such tumors, because of their shape, have been described as "dumbbell" or "hourglass" tumors Enlargement of the vertebral foramina in association with a mediastinal density is a helpful roentgenographic sign for diagnosis.

The neurofibroma has the same characteristics It is distinguished histologically by having all the elements of a nerve trunk, instead of only sheath cells Sheath cells are the predominant type, but an orderly arrangement of the cells as found in the neurilemmoma is lacking This finding is the main distinguishing feature

Ganglioneuromas occur more frequently in the posterior mediastinum than elsewhere in the body These tumors are relatively uncommon They may attain a large size, present "hourglass" features and cause pressure on the spinal cord Histologic examination shows ganglion cells and satellite cells in a "rosette" formation They are invasive in nature and for this reason, among others, are thought sometimes malignant Stout has classified the ganglioneuromas as (1) fully differentiated tumors that do not metastasize, (2) partly differentiated, in which differentiated and undifferentiated cells are mixed together, and which occasionally metastasize, (3) tumors

containing both nodules of fully differentiated ganglioneuroma and nodules of sympathicoblastoma and which metastasize in the majority of instances This type of tumor occurs in young people, *whereas most neuroblastomas are found in adults*

Sympathicoblastoma is an embryonal tumor. This neurogenic tumor also occurs in the posterior mediastinum. It is usually *found in young children*, rarely in adults. Metastases develop early and involve bone, lymph nodes, liver and lungs.

Paraganglioma and pheochromocytoma are tumors originating from chromaffin cells All are rare; one paraganglioma and four mediastinal pheochromocytomas have been reported. The pheochromocytomas give similar clinical features with hypertensive episodes like those tumors found in the adrenals. Aortic body tumors are mentioned to complete the list of neurogenic tumors, but they are most rare.

Malignant schwanoma also occurs in the posterior mediastinum This tumor is composed of Schwann cells; it does metastasize. Rarely, the origin will be in peripheral nerves or the vagus nerve. Byron has reported a neurofibroma of the vagus and one has been encountered in a personal series of mediastinal tumors (see fig 3)

The majority of neurogenic tumors are benign, and after removal, survival and lack of recurrence is the general rule.

Teratodermoids

The usual location of these tumors is in the anterior mediastinum (see *figure* 1). *It is the most common anterior mediastinal tumor.* They deserve the first consideration when an abnormal roentgenographic density appears in the anterior mediastinum. Their embryologic origin results in their anterior location in front of the pericardium and the great vessels. This intimate relation adds to the hazard of their surgical removal Two cases located in the posterior mediastinum were seen and three reports have been made of locations other than the anterior mediastinum. These instances are rare events

The distinction between teratomas and dermoids have been made by some authors This classification into two groups appears to be rather difficult because there are gradations between *the so-called dermoid cyst*, lined by epidermis with its appendages, often including hair, and the complex teratomas which are composed of derivations of all the germ layers Of the entire group, *at least 90 per cent are benign; the other 10 per cent of the teratodermoids with the more complex histologic features and solid mass are malignant.*

The occurrence is equal for the sexes. Teratodermoids are more frequent *in children and young adults* The teratodermoids tend to increase in size

during adolescence and early adult life, and because there is little room for them to expand between a rigid sternum in front and the pericardium behind, they frequently cause symptoms resulting from pressure. Dyspnea, palpitations and substernal pain are common These complaints may be progressive, or a silent period may follow, or again all symptoms may have been absent

Infection is a common complication which may cause symptoms not previously present Malaise and fever are symptoms whose origin may be unrecognized If the infection causes rupture into the bronchus, the pleural space or the pericardium, a grave situation will result On occasion, a bronchial fistula is produced, expectoration of sebaceous material and hair signals this occurrence and indicates the diagnosis Hemorrhage into the pleural space or the pericardium are other serious complications.

Discrepancy between subjective symptoms and the objective finding of an anterior mediastinal mass suggests the diagnosis of teratodermoid The presence of calcified teeth or bone in the mass is almost specific The presence of atelectasis, pneumonitis and pleural effusion may partially or totally obscure the radiologic visualization of the dermoid It has been reported as an intrapericardial tumor which creates even greater difficulty for diagnosis

If serial chest roentgenograms show a rapid rate of growth, the tumor is almost certainly malignant, but a sudden increase in size within a few days is usually due to hemorrhage and infection The recognition of satellite spheroid densities on the chest roentgenogram is invariably a finding associated with malignant teratodermoids

Pericardial Coelomic Cysts

These cysts are not uncommon Abnormalities of the development at the time of formation of the primitive diaphragm are considered the origin They are situated anteriorly, and often near the cardiophrenic angle Three-fourths of them are found on the right side They are frequently difficult to differentiate from other anterior masses They are thin-walled cysts containing clear fluid and lined by a single layer of endothelial cells Because of the crystal clear fluid they have been called "spring water cysts" Some are attached by a pedicle to the pericardium This type is often movable and changes location One has been described in the upper mediastinum with a long pedicle attached to the usual place on the pericardium Diverticula of the pericardium are related and give the same roentgenographic appearance Usually they cause no symptoms being but a radiologic finding; however, large cysts by pressure may cause dyspnea Occasionally, they become infected, they may resemble a diaphragmatic hernia Since they are difficult to differentiate from other masses occuring in the mediastinum, their removal is recommended (see figs 4 and 5).



Fig 4—The posterior-anterior film of a 20 year old male who was found to have an irregularity of the left cardiac border The lateral film did not show any abnormalities On removal this was found to be a pericardial cyst containing clear "spring water" fluid

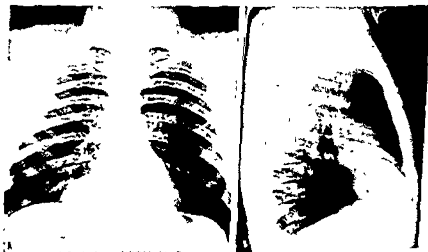


Fig 5—(A and B) A typical radiologic appearance for a pericardial cyst in a young male patient *The most common location is at the right side*

Thymomas

Thymomas may be solid tumors, benign or malignant They are usually highly invasive tumors but may be encapsulated Recurrence is not uncommon even with tumors thought to be completely removed Although it is thought the thymic cyst is rare, almost one-half of the thymomas seen by the author were cysts In the thymic cyst, hemorrhage is common and causes sudden enlargement with the production of symptoms

In malignant thymomas, symptoms are usually prominent. fever, substernal pain, cough and weight loss Patients with these and other anterior mediastinal tumors may complain of angina, and have electrocardiographic changes simulating a myocardial infarction due to interposition of tumor between chest wall and heart

On the plain frontal roentgenogram of the chest the tumor is obscured by the sternal shadow unless it is very large It may then appear as a lobulated mass on one or both sides of the mediastinum The lateral film will usually show a density lying between the sternum and upper mediastinum (figs. 6–8) Tomography will be of further help Angiocardiography is of distinct aid in showing the location, extent and vascular invasion present. It also rules out an aneurysm In contrast to retrosternal goiters, the convexity of the upper pole of the tumor is visible on the x-ray examination and does not move upward on swallowing Thymomas are not palpable in the neck

There are two clinical presentations in disorders of the thymus gland, which need discussion Myasthenia gravis has not personally been seen. This is in keeping with the observation that 85 per cent of the patients with myasthenia gravis exhibit no discernible abnormality in the thymus gland Symptoms may not appear for years after the detection of the tumor This may be the reason that myasthenia gravis is not noted in most patients Although some surgeons believe that removal of the tumor will relieve the myasthenia, consistent results have not been obtained, in fact some reports have stated that symptoms have in fact become worse and uncontrollable For the myasthenic patient the use of radiation therapy before surgery has been stated to give better results

The other clinical state associated with thymoma has been reported a number of times A severe anemia with an aregenerative or aplastic marrow has been noted which becomes completely corrected after removal of the tumor. This very fascinating association has not been fully explained

All thymomas should be regarded as malignant tumors and therefore should be removed early after their discovery. Preoperative radiation is recommended by some, and certainly postoperatively if a thymoma is discovered at operation When myasthenia gravis is present, higher dosages of neostigmine should be given preoperatively and muscle paralyzants avoided for operation Postoperative care must be scrupulous and neostigmine requirements constantly estimated



Fig 4—The posterior-anterior film of a 20 year old male who was found to have an irregularity of the left cardiac border The lateral film did not show any abnormalities On removal this was found to be a pericardial cyst containing clear "spring water" fluid.



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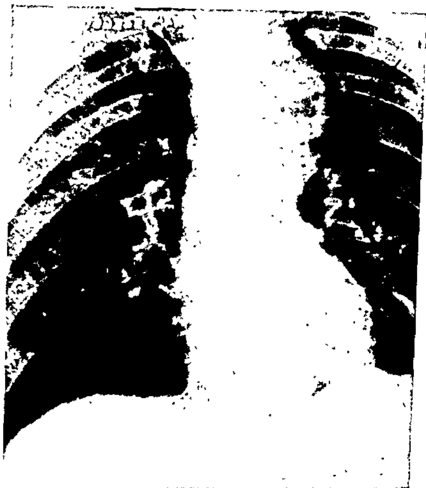


Fig 6—A thymoma presenting mainly in the left side of the upper mediastinum in a 32 year old male patient

Intrathoracic Goiters

Aberrant location of the thyroid gland is not an uncommon cause for an upper mediastinal mass An incidence of 0 8 per cent of the intrathoracic location of 11,800 thyroidectomies has been reported by Crile.

Intrathoracic goiter is a common tumor of the anterior mediastinum and is found in the upper portion A colloid goiter needs only to increase slightly in size to become partly or wholly retrosternal in location. Seven to twenty per cent of all cervical goiters operated on extend to or are just beneath the sternum Some goiters disappear spontaneously and are later identified in the thorax The totally intrathoracic goiter, which cannot be felt in the neck, is much rarer than the partially intrathoracic goiter. Very rarely the goiter which disappears from the neck may suddenly come back into view; this

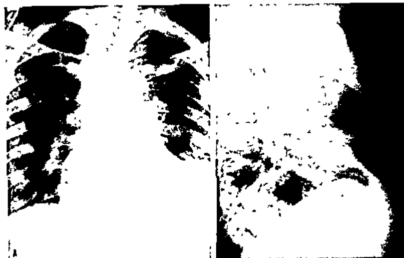


Fig 7—(A and B) A thymic tumor situated in the anterior upper mediastinum There were no myasthenic symptoms There were considerable pressure symptoms associated with the tumor



Fig 8—The frontal view of the roentgenogram in 20 year old white male There were marked symptoms of dyspnea, chest pain, fever and loss of weight This proved to be a malignant thymoma

interesting finding has been termed "plunging" or "bobbing" goiter. If the goiter is not palpable by the classic maneuver of swallowing with head slightly flexed forward, then the performance of the Valsalva maneuver may pop it back into the neck Patients suffering with this form of goiter use this method to relieve themselves of pressure symptoms.

Although most intrathoracic goiters do not produce symptoms, substernal distress, dyspnea and respiratory embarrassment do occur. Characteristic frightening spells of coughing from the pressure on the trachea are a chief symptom. Distension of cervical veins may be noted when mediastinal compression is present.

The roentgenogram of the chest will show the abnormal density in the upper mediastinum, and the trachea is usually displaced to one side or the other The trachea is also narrowed and flattened from in front in the severer forms of pressure (figs. 9–11) The thoracic outlet at this point is limited and rigid and pressure is common. The roentgenographic examination during a Valsalva maneuver may demonstrate the disappearance of the mass from the mediastinum.

If a palpable goiter in the neck or a previous thyroidectomy scar are absent, palpation in the suprasternal notch or supraclavicular fossae of a retrosternal mass on swallowing or deep inspiration, upward movement of the mass on swallowing, the presentation of a mass on the roentgenogram with a sharp convex edge but poor definition of its upper pole, radioactive iodine uptake over the mass, the presence of patchy calcification within the mass, are all helpful clinical signs. A scintillatogram may be negative if the gland is nonfunctioning. Although these diagnostic points are not infallible, they may be helpful to decide the operative approach. Removal by a cervical approach is the choice of treatment whenever possible

Rarely the intrathoracic substernal goiter may be found posterior to the trachea and esophagus (Lahey, Sweet, von der Lieth and Lester).

Granulomas

Granulomatous inflammatory disease commonly presents as hilar and upper mediastinal enlargement (fig. 12A and B) This roentgenographic appearance resembles lymphoma. In instances of tuberculosis, histoplasmosis and sarcoidosis where there is a characteristic bilateral hilar and paratracheal lymph node enlargement associated with pulmonary parenchymal involvement, the distinction from other mediastinal lesions is relatively easy An atypical silhouette on the radiologic examination may be confusing Unilateral hilar enlargement alone can be troublesome, for in older patients it suggests bronchogenic carcinoma. Temporary enlargement of the mediastinal nodes may accompany whooping cough, measles and erythema multiforme Sometimes the enlargement may be great enough to compress a bron-

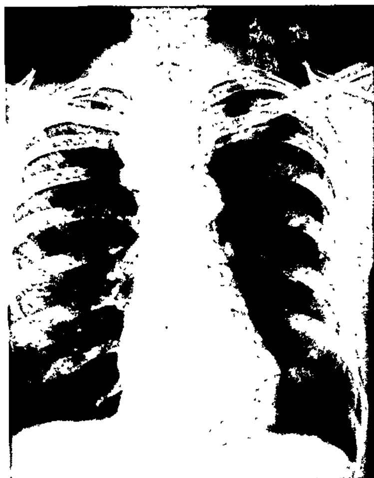


Fig 9—The frontal plain chest film of a patient with a typical radiographic appearance of a simple goiter The angiocardiographic study showed the displacement of the innominate artery laterally and anteriorly, with the superior vena cava displaced far laterally Note the displacement of the trachea to the left A radioiodine scintillogram was negative because of an inactive gland

chus and cause lobar atelectasis Metastatic enlargement may occur from carcinoma

Scalene node biopsy is most helpful, and any associated clinical findings strengthen the diagnosis of a granulomatous disease Scalene node biopsy has established the diagnosis in 60 to 75 per cent of patients with this type of mediastinal disease and who did not have other helpful findings Thoracotomy may be resorted to if none of the other findings are present



Fig 10—The plain posterior-anterior chest film of a widening of the right superior mediastinum Note that the trachea is not deviated. A radioiodine uptake was not detected over this mass The lateral chest film shows the mass to be in the upper mediastinum Note that the upper borders of the mass are indistinct At operation an intrathoracic colloid goiter was removed

In granulomas due to infection, the presence of parenchymal fibrosis and calcifications may be helpful *In tuberculosis, there is a definite predilection* for involvement of the lymph nodes where the azygos vein joins the superior vena cava Storey and Lyons, and Kunkel reported that tuberculomas usually present as smooth, oval or rounded, lobulated masses adjacent to the trachea and protruding into the right thorax (fig. 13A and B). However, other tumors, right-sided aortic arches, neurofibromas and even lymphomas have this appearance. Although thoracotomy may become necessary for accurate diagnosis, removal is difficult, because of the dense inflammatory reactions associated with granulomas Involvement with fibrous adhesions may result in injury to the phrenic nerve, superior vena cava, trachea and other structures For this reason, the diagnostic routine *should be thorough;* if the diagnosis is established, the indicated therapy can be used. The therapy may actually be specific. Judgment may dictate an empiric employment of therapy, for example, antituberculous drugs before resorting to a thoracotomy to establish a histologic diagnosis in a suspected probable tuberculous disease

In all mediastinal processes it is absolutely necessary to make a contrast examination of the esophagus, even though the medical history fails to record symptoms attributable to the esophagus. The x-ray study not infre-



Fig 11—(A) The posterior-anterior film of a 62 year old negro female who had a history of a thyroidectomy performed 10 years previously There is a large mass occupying the whole upper two-thirds of the right chest Note the scattered areas of irregular calcification throughout the density A scintillogram showed uptake of radioactive iodine over the whole area

quently reveals a shift of the esophagus or demonstrates the impressions on the esophageal lumen by glands or vessels It also may demonstrate an unsuspected achalasia of the esophagus which is the cause of the mediastinal abnormality

Metastases may produce mediastinal masses and are reported as most common with pancreatic and gastric carcinomas, but in the younger patients, testicular tumors are the most frequent cause Diagnosis can be established by history and clinical findings The scalene node biopsy is most fruitful in this type of problem Diaphragmatic hernias sometimes are confused with a mediastinal tumor The hernias which simulate a mediastinal



Fig 11—(B) The lateral chest film shows the mass to be mainly anterior with its upper margins indistinct and it is extending also into the posterior mediastinum behind the esophagus Note that the trachea is not deviated but compressed in the anterior-posterior diameter At operation a large adenomatous intrathoracic goiter was removed

tumor are frequently those which come through the foramen of Morgagni, or an abnormal esophageal hiatus. The recurring burning pain and dyspepsia should rouse suspicion for proper radiologic investigation to be done.

Pharyngo-esophageal diverticula will occasionally have to be differentiated from other cysts as they may attain considerable size and enter the superior mediastinum.

Mediastinal pleural effusions may simulate a tumor (fig. 15). These effusions are found in infections and cardiac failure. They are "vanishing" tumors for they will disappear as the causative condition improves Their consideration should be held whenever a patient has one of the conditions mentioned.



Fig 12—(A) Posterior-anterior chest film of a patient with sarcoidosis Note the large hilar and paratracheal densities

Aneurysms and Abnormal Vascular Masses

An angiocardiogram is essential for the proper evaluation of a mass which causes suspicion of a vascular abnormality. Angiocardiography can distinguish a vascular from an avascular lesion In clinics in which this procedure is not employed, exploration may be done for diagnosis of a mediastinal tumor Operations have been performed in error for right-sided aorta, dilated large left auricle, coarctation of the aorta (poststenotic dilatation), aneurysms of the innominate artery, common carotid artery, ascending transverse and descending aorta, and pulmonary artery. Cystic azygos lobe tumor should be recognized by its position

With the advent of angiocardiography, vascular lesions can be recognized and corrective operations planned Demonstration of irremediable vascular lesions is also possible

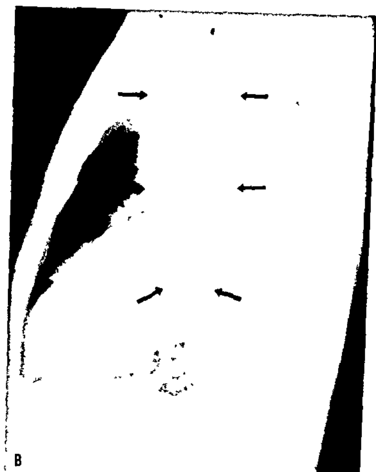


Fig 12—(B) Note that on the lateral films the densities are present in the middle mediastinum, the usual place for granulomatous disease

Reports in the literature show the need for a thorough study including angiocardiography before surgical exploration. Vascular anomalies and abnormalities can simulate a mediastinal tumor; the converse is also true and only opacification of the vascular system will distinguish between the two situations

Lipomas

The lipomatous tumors are rare. they may be benign (the more common), or malignant, as a sarcoma. The radiographic appearance of a more radiolucent type of shadow suggests a lipoma. A translucent periphery is a valuable roentgenographic sign when present. Some of the lipomas have an "hourglass" appearance representing an intrathoracic and extrathoracic portion. This characteristic may be observed in (1) cervicomediastinal tu-

mors passing from mediastinum into neck, and (2) transmural—passing through the chest wall, through the intercostal space and, rarely, through the sternum or diaphragm

The intrathoracic type of lipoma may be asymptomatic and its discovery depends on the disclosure of a shadow on the routine chest films Any symptoms are those of pressure on mediastinal structures

The abnormal shadow may be confused with a pericardial effusion or cardiac enlargement The "hourglass" appearance is characteristic and if seen will help the diagnosis

Bronchogenic Cysts

These tumors are not rare and characteristically are usually located in the posterior part of the superior mediastinum at the level of the tracheal bifurcation Usually asymptomatic, they may be an incidental finding at autopsy In infancy and early childhood, bronchogenic cysts may produce serious tracheobronchial obstruction

Maier has classified bronchogenic cysts into four groups on the basis of their location.

1 Paratracheal—attached to the tracheal wall usually on the right just above the bifurcation
2 Carinal—attached to carina and anterior esophageal wall
3 Hilar—attached to one of the main or lobar bronchi
4 Paraesophageal—the cysts are in intimate relationship with the esophagus and may have no connection with the tracheobronchial tree

The cysts are filled with a milky mucoid material desquamated epithelial cells.

It is generally accepted that these cysts arise as embryonic derivations of the budding foregut, and this origin is in accord with their location Maier also advances a possible interrelationship with tracheal diverticulas and tracheo-esophageal fistulas

These cysts may be mistaken for neurogenic, dermoid and pericardial cysts, as well as intrathoracic goiters They may move on swallowing, and may be occasionally palpated in the neck as a smooth soft mass A sudden increase in size may cause dyspnea, dysphagia and venous obstruction Hemoptysis is a sign that infection is present Infection is common These lesions may be unrecognized when located behind the heart and for this reason overpenetrated Bucky films and lateral films are important for complete study (fig 14A and B)

Miscellaneous Types

There are other mediastinal tumors which are less common, chylous cysts, myxomas, fibromas, xanthofibromas, chondromas, plasma cell myelomas

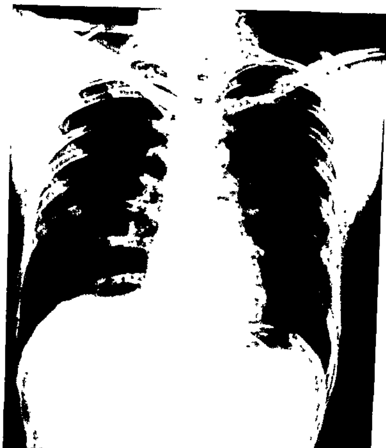


Fig 13—(A and B) A rounded spherical density in a 19 year old male which is located in the upper and the middle mediastinum This proved to be tuberculosis

and meningoceles Hemangioma, lymphangiomas and parathyroid adenoma are very rare tumors Four mediastinal pheochromocytomas have been reported.

Gastroenteric cysts are rare. They are usually located along the spine in the posterior mediastinum. Intestinal mucosa is found in most and often is accompanied by peptic ulceration The male sex predominates. The majority are found in early life up to 4 years of age. Slight chest pain and dyspnea are the clinical symptoms Bronchial compression has been seen with large cysts of this type Scoliosis has been noted with the large-sized cyst and long-standing pressure

Discussion

The mediastinal tumors may be a source of confusion in differential diagnosis It is axiomatic that only by microscopic examination of the excised



Fig 13—(B) *See legend, facing page*

specimen, or a portion thereof, can an accurate histologic diagnosis of a mediastinal tumor be made However, a number of diagnostic procedures are available which may yield valuable information in the study of a mediastinal abnormality An orderly investigation, even in the absence of establishing a definite diagnosis will commonly indicate the proper therapeutic approach, whether it be surgery, irradiation, drug or chemical therapy or a further period of observation

The diagnostic procedures recommended are listed in table 2 The roentgenographic examination is the most important and gives the greatest yield. The radiologic studies usually demonstrate the probable nature of the lesion Special films and fluoroscopy are important. The knowledge of the common locations and characteristics of the various neoplasms and nonneoplastic masses found in the mediastinum assists the institution of the proper investigations Preoperative diagnosis is more accurate in tumors with known radiologic characteristics such as the lymphomas, neurogenic tumors and teratodermoids Even these may at times present atypical features. The experienced investigator is alert to recognize other lesions

aids may prevent needless exploratory thoracotomy. Angiocardiography informs about the feasibility of operation or evidence to contraindicate an operation.

Thoracotomy is mandatory and must not be delayed when the diagnosis cannot be established by less formidable methods. Thoracotomy enjoys a low case fatality rate, offers a cure in benign lesions and provides accurate information of the histologic nature and the gross involvement by the tumor This permits intelligent management and provides valuable information for prognosis

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multiple myeloma with its differing degrees and features of bone lesions, to rare cases of plasma cell leukemia. As concerns the chest, the more common lesions are in the bones; less common are plasma cell tumors of the soft parts or viscera.

Leukemias are usually discussed along with malignant lymphomas Some of the lymphomas, namely the various forms of lymphosarcoma and rarely plasma cell myeloma, may develop a leukemic picture. Perhaps questionably, true Hodgkin's disease may extremely rarely develop a picture of monocytic leukemia Naturally, any of the leukemias, such universal diseases, may present important lesions of the structures of the chest

Thymomas will be discussed in another chapter.

Anatomic Varieties

The malignant lymphomas of greater numerical importance affecting structures of the chest are Hodgkin's disease and lymphosarcoma In general their lesions within the thoracic cavity are much alike and therefore may be discussed together, noting a few differences

Intrathoracic Lesions

Enlargement of mediastinal nodes is one of the most common early intrathoracic lesions of Hodgkin's disease or lymphosarcoma This enlargement may be the first sign of the disease and in not a few cases is discovered unexpectedly by x-ray examination of the chest done for one reason or another, when no symptoms have been noted Even large mediastinal masses are sometimes discovered in this way. There is in some cases first a slight enlargement of right paratracheal nodes In other cases there may be an appearance of straightening of the left border of the cardiac shadow, suggesting enlargement of the pulmonary conus and this may be mistaken for the peculiar cardiac anomaly (fig 1A and B) The full-blown picture of mediastinal malignant lymphoma is usually of a superior anterior mediastinal mass showing on the PA chest films as a mediastinal shadow unmistakably wider than normal with smooth, scalloped or fuzzy borders, either symmetrically placed or extending more to one side (fig 2). On the lateral chest film there is seen a density above the heart shadow Percussion anteriorly may reveal not only a widening of the mediastinal area of dullness but an increased intensity of dullness over the upper half of the sternum. Some cases present initially or occasionally later in the course with a moundlike elevation over or alongside the sternum.

Only a hilar prominence may be seen, unilateral or bilateral. This may be difficult of interpretation as to whether it really represents nodal enlargement. Rarely a bilateral hilar nodal enlargement is so symmetric in a relatively asymptomatic patient, as to suggest sarcoidosis.

Compression of the superior vena cava and its tributaries, results in the superior caval syndrome with dilatation of veins on the chest wall and in

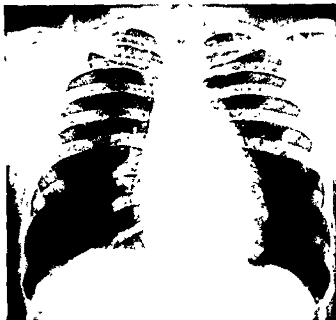


Fig 1—Patient J G (A) December 8, 1950 "Question of some anomaly of pulmonary vessels" (left groin node thought caused by epidermophytosis)



Fig 1—(B) October 3, 1951 Increase of the mediastinal mass (the left groin node then biopsied showing Hodgkin's disease)

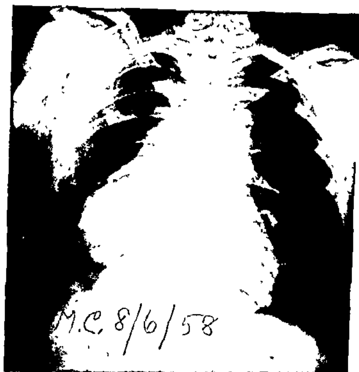


Fig. 2—Patient M C Unilateral extension of mediastinal sarcomatoid Hodgkin's disease

the upper extremities and neck, congestion and puffiness of the face and neck, puffiness of eyelids, most marked in the morning and sometimes edema of one or both arms Thrombosis of some part of the affected venous system may complete the picture.

Paralysis of the recurrent laryngeal nerve or the phrenic nerve may occur, although less commonly than with bronchogenic carcinoma.

The mediastinal lymphomas, especially Hodgkin's disease and reticulum cell sarcoma, may closely simulate bronchogenic carcinoma clinically and vice versa. The oat cell bronchogenic carcinoma may produce a fairly smoothly outlined mediastinal mass that roentgenographically looks like a lymphoma. The lymphomas may show greater enlargement on one side of the mediastinum with a shaggy lateral border and streaky infiltration extending out into the adjacent lung field, quite suggestive of bronchogenic carcinoma Furthermore, the patient with a mediastinal lymphoma may have some hemoptysis Occasionally, a diagnosis of Hodgkin's disease has been made by bronchoscopic biopsy. The first known report of such a biopsy was made by Lee M Hurd of New York City in 1922.

In the patient presenting only a mediastinal mass with no significant supraclavicular or axillary nodes, the accomplishment of a differential diag-

nosis may be difficult and only obtainable by exploratory thoracotomy. A scalene node biopsy may be done and yet fail to yield diagnostic material

The simulation of goiter by mediastinal and low anterior-cervical malignant lymphomas is occasionally experienced In some instances it has not been until a planned surgical exploration of the thyroid was started that the true diagnosis was discovered. In one case first seen by me about a month following such an operation at a large university hospital, it was of interest to see the record of the radiologist's interpretation of the chest films and the surgeon's comment at the time of his exploration of the thyroid region and partial resection of the mass that extended into the mediastinum The radiologist's conclusion was "consistent with a very marked substernal extension of the thyroid " The surgeon's comment at the end of his dictated report of the operation was "This is some unusual and peculiar tumor which fits best into 'carcinoma of lateral aberrant thyroid' and of 'left lobe of thyroid gland ' The prognosis is grave because excision is impossible and probably it is not susceptible to radiation therapy." Figure 3 shows the appearance of the chest film 36 days after the operation

As Hodgkin's disease or lymphosarcoma of the mediastinum progresses

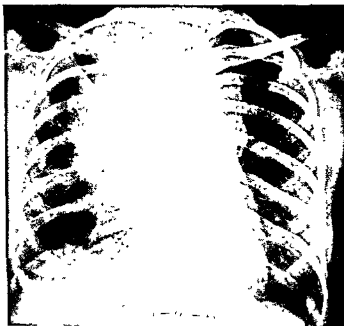


Fig 3—Patient D V F Large cervical and intrathoracic Hodgkin's disease which only 36 days previously had been considered by the radiologist and the surgeon who explored the neck to be an unusually large thyroid tumor

without treatment or as they recur following regression brought about by treatment, various types and degrees of invasion or spread to other tissue or organs of the chest develop. There may be found on x-ray films at first a streaky infiltration extending out from the hilum or edge of the mediastinum This may progress to an extensive infiltration of the lung with or without evidence of atelectasis. Nodular or patchy infiltrates may arise in the lung parenchyma. These may lie well out in the lung field, having no obvious direct connection with the mediastinal lesion, suggesting a hematogenous mode of spread or a spread by invisible permeation of lymphatics Bronchial or bronchiolar occlusion may lead not only to local atelectasis or emphysema but also to abscess formation distal to the obstruction. Particularly in Hodgkin's disease may one occasionally find small or large, single or multiple cavities within parenchymal deposits, perhaps caused by central necrosis and sometimes occurring with no obvious evidence of infection and prior to any irradiation of the regions so affected (fig 4).



Fig 4—Patient P C Cavity in posterior portion of right lower lobe of lung, 8 cm in diameter with its wall composed of fibrous and tumor tissue was found at post-mortem 2½ months later.

There is an area of considerable diagnostic uncertainty in the roentgenographic interpretation of either tiny single or numerous small nondescript slight densities that may appear within the lung field in known cases of malignant lymphomas It may be impossible even for a long time and with serial roentgenograms and examination of sputum to know whether these little shadows mean deposits of the malignant lymphoma or some inflammatory process

The use of corticosteroids and ACTH, now so prevalent in the treatment of the more advanced cases, is followed in some instances by the more or less quiet appearance of a pneumonitis or lung abscess

Rather common in present day treatment of the malignant lymphomas, in cases in which there has occurred repeated activation of intrathoracic lesions, is the problem of how much of what is seen as abnormal densities in the chest films represents active disease, and how much is caused by radiation induced exudative or fibrotic changes The risk of pulmonary fibrosis must always be taken into account when considering the factors of total dosage of radiation, crossfiring of beams, and particularly in retreatment of chest fields One advantage of the alkylating agents is that they do not cause fibrosis Yet, there are instances in which the use of an alkylating agent may seem contraindicated by reason of serious marrow depression, and in which it seems possible that some temporary partial regression might be achieved by further irradiation of a field that is thought to present active disease, together with fibrosis resulting from previous irradiation Since it may be possible to give radiation therapy to such a local region without materially endangering the patient with respect to the marrow depression, and yet in time if the patient lives long enough, further fibrosis is likely to be added, one may sometimes deliberately decide, in order to try to relieve distressing symptoms, to "sacrifice the future for the sake of the present"

Pleural effusion is common in the malignant lymphomas The simplest form is a unilateral transudate associated with mediastinal and hilar lymphoma Rarely will such an effusion clear spontaneously. Often treatment of the underlying mediastinal and hilar lymphoma by radiation alone will lead to disappearance of the effusion It has been the writer's preference to try such treatment first in a case in which the effusion has appeared either accompanying a previously untreated mediastinal lymphoma or in a case having not had a great amount of prior irradiation to the chest, and not to resort immediately to thoracentesis If the effusion does not clear within a reasonable time of a month or two, or of course if it is massive, thoracentesis is indicated The fluid should be thoroughly examined for specific gravity, cell content and bacteriologic culture

If the fluid has the characteristics of an exudate containing blood or a high number of cells, or is fibrinous, clotting rapidly and having a high specific gravity, the suspicion is probably justified that there are pleural plaques

or nodules of the lymphoma In that case the treatment should be accordingly devised to exert effect on the pleura and lung of that side. Treatment by irradiation may be effective, or *one may choose to try the effect of intra*pleural instillation of radioactive gold (Au^{198}), radioactive phosphorus (P^{32}) as chromic phosphate, or nitrogen mustard (HN2). However the impression of the Medical Neoplasia Service of Memorial Center has been that the effect of nitrogen mustard on the pleural effusions of lymphoma cases is often more like that of intravenous administration and less effective locally in causing pleural tumor regression and disappearance of effusion than in cases of pleural effusion caused by some metastatic carcinomas and sarcomas.

A milky *effusion proved by content of fat to be genuinely chylous indi*cates involvement of the thoracic duct. In general it has been difficult if not impossible to succeed in clearing a chylous effusion.

The circulatory system within the chest may not only be affected by pressure on the superior vena cava and its tributaries, but there may rarely be actual invasion and erosion of the walls of great vessels The pericardium and the myocardium are by no means immune to lymphomatous lesions, either by invasion from contiguous structures or presumably by hematog*enous spread, (or possibly by lymphomatous lesions arising de novo).* Pericarditis and pericardial effusion seem somewhat more common than tumor formation in the pericardium or myocardium. Myocardial nodules may give signs and symptoms and electrocardiographic findings like those of cardiac infarction If the diagnosis of actual invasion of the cardiac structures by malignant lymphomas seems fairly certain, radiation therapy to that region may be strikingly helpful in some cases and possibly safer with the present practice of divided dosage than the rapid tumor-destroying effect that might result from a full-dose injection of nitrogen mustard.

The esophagus may become implicated in any part of its course. Its wall may be extensively invaded by the lymphoma. In some cases there may develop an *extensive esophagitis, and although symptoms and radiographic*
[illegible] esopha-
ion
um

or into some adjacent part of the bronchial tree (fig. 5).

Any part of the chest wall may show lesions of a lymphoma In cases of plasma cell myeloma the bony structures may show the characteristic multiple punched-out osteolytic foci. Rarely may a slight blastic change be noted about the periphery of some of these lytic lesions. There may be fractures of ribs or collapse of vertebrae. Occasionally, in myeloma the appearance may be that of osteoporosis, while in some cases in which the diagnosis can be established by marrow examination, electrophoresis and immunologic tests, the bones may appear normal radiographically.

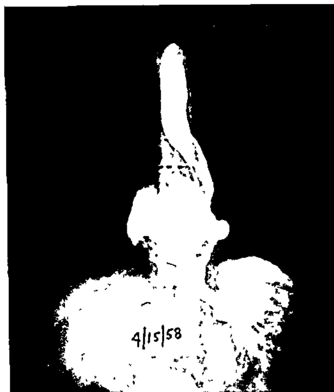


Fig 5—Patient J E Fistulous tract from esophagus into mediastinum in Hodgkin's disease Diagnosis established by biopsy from esophagus nearly 2½ years earlier

In the bones, Hodgkin's disease and lymphosarcoma may produce lytic or blastic lesions Lymphosarcoma is more likely to produce lytic lesions, while in Hodgkin's disease the most frequent type of lesion is a combination of blastic and lytic change The least common type of Hodgkin's lesion in bone is the pure blastic change, occasionally demonstrated by a single vertebra having an ivory-like density.

It is not rare to palpate a firm, fixed fusiform enlargement of a rib, seemingly unquestionably representing a true lesion of the rib, and yet to be unable to see on x-ray films any evidence of a rib lesion On the other hand, rib lesions may be visualized on x-ray films with or without palpable tumors of the ribs or local tenderness or pain over them. Their involvement may come about through hematogenous spread or by direct invasion from adjacent pleural lymphomatous disease In advanced cases one may have a massive lymphomatous tumor implicating and binding together lung, pleura, ribs, intercostal tissues and perhaps even the overlying skin.

The skin and subcutaneous tissues of the chest wall may of course show many of the characteristic lesions of mycosis fungoides. These may vary from patches of eczematoid change or psoriasiform lesions, to a diffuse erythroderma, to flat or raised plaques or masses of reddish color, with or without ulceration.

The characteristic skin lesion of lymphosarcoma is a raised pinkish red plaque, feeling moderately firm. It may vary from a centimeter or less in diameter to several centimeters. Ulceration is rare but may occur. The skin lesions of Hodgkin's disease vary considerably. Occasionally, multiple small shotty subcutaneous nodules with or without a little invasion of the overlying skin may be palpated. These have seemed to be more common about the upper anterior chest wall Rare cases may present single or multiple discrete, firm, raised nodules, or they may be centrally broken down and soft, resembling infected sebaceous cysts, and may ulcerate. Rarely, single or multiple cold abscesses like those of tuberculosis may be simulated In other rare cases, there may be broad sheets of erythematous skin infiltration, sometimes with serpiginous ulceration

Concomitant nonspecific lesions of the skin are frequently seen in patients with lymphomas. Herpes zoster is an almost routine complication at some time during the course Occasional cases will show generalized herpes in addition to the zonal rash The question of cross infection with chicken pox is of interest in cases of herpes zoster but usually one cannot establish a history of exposure to chicken pox

Kaposi's multiple idiopathic hemorrhagic sarcoma of the skin is seen just often enough in cases of malignant lymphoma to raise the question of its *histogenetic relationship. In Hodgkin's disease particularly,* it is not so rare to see xeroderma or an exfoliative dermatitis or patches of dry eczematoid [illegible] skin [illegible] pear. [illegible] egree of gynecomastia is noted The breast, male or female, may develop a nodule or nodules of lymphomatous disease secondarily. *Occasionally, the first diagnosis* of lymphosarcoma has been made by local excision or even mastectomy for a firm nodule found within a woman's breast

Diagnosis

The only proof of Hodgkin's disease, any type of lymphosarcoma or mycosis fungoides, is by biopsy. Depending on the clinical setting, a biopsy may be obtainable from various sites. some lymph node, most commonly in cases of Hodgkin's disease or lymphosarcoma; some other tissue such as skin or bone, some viscus such as stomach, bowel or lung, less commonly in cases of Hodgkin's disease or lymphosarcoma. In mycosis fungoides the

biopsy is naturally usually from the skin In plasma cell myeloma a marrow aspirate is often diagnostic. It has become increasingly evident that on bone marrow aspiration the presence of a moderate increase in plasma cells is not necessarily diagnostic of myeloma, but may be found in association with various other diseases Bence-Jones proteinuria may not be found in more than one-third to one-half the cases of proved plasma cell myeloma On the other hand, the diagnosis of myeloma may be reasonably well established by a combination of laboratory findings (elevated serum protein with high globulin, the characteristic myeloma spike in the electrophoretic pattern and a characteristic immunologic pattern as described by Korngold)

In cases of lymphosarcoma (including reticulum cell sarcoma) or Hodgkin's disease producing a mediastinal mass there will often be palpable nodes or a node above the clavicle or perhaps in the axilla, recognizable as probably significant for biopsy by reason of firmness, globularity or irregularity In cases presenting a partial or full-blown picture of the superior caval syndrome, *the neck especially in the supraclavicular regions and sometimes the* axillae may be so puffy that nodes cannot be distinctly or at all palpated In some such cases biopsy of a palpable node shows only a hyperplastic change Not infrequently, cases with the superior caval syndrome present no suitable peripheral nodes for biopsy and produce no diagnostic cells in the sputum Thus the diagnosis remains uncertain as between a malignant lymphoma and a bronchogenic carcinoma or some other space-occupying neoplasm in the superior mediastinum Since such patients are seldom if ever suitable for exploratory thoracotomy, and yet may be given striking palliation if treated properly on an emergency basis, this is one setting in which treatment of neoplastic disease without proof of diagnosis is justified The most efficient method of treatment of the neoplastic superior caval syndrome is to give a full intravenous dose of nitrogen mustard (0 4 mg /Kg body weight) followed without more than a day or two of delay by fractionated high voltage (250 kilovolts) or supervoltage (1,000–2,000 kilovolts) roentgentherapy to the mediastinal mass through straight anterior and posterior fields mapped out to correspond to the size and shape of the mediastinal mass Usually about 200 roentgens in air will be given to one port a day treating the 2 ports alternately until from 2,000 to 3,000 roentgens in air has been delivered to each port

There is no evidence that biopsy disseminates malignant tumors There should be no hesitation, therefore, in insisting on biopsy when it is possible to obtain one without danger to the patient whose thoracic neoplasm has not been identified previously As in all treatment of neoplastic disease, only under exceptional circumstances, for example the superior vena caval syndrome just described, is it good practice to apply treatment without knowledge of what is being treated It is still too common a practice to start a course

of radiation therapy to a mediastinal mass that looks like a lymphoma out biopsy proof even though a means of such proof exists. Modern tho surgery justifies exploratory thoracotomy in most cases of medias tumor or lung tumor when proof of diagnosis cannot be obtained in other way. The exploration will usually at least obtain a positive bio Although usually a malignant lymphoma cannot be completely rese *from the mediastinum*, sometimes that has been possible, or at least a l part of the mass may be resectable, leaving less to be treated. Naturall a peripheral node is available in the supraclavicular or axillary regio association with a mediastinal or lung tumor and proves to be positive a malignant lymphoma, it may be fairly safely assumed that it repres the nature of the intrathoracic lesion with but few exceptions, and in case thoracotomy is not advised

If a patient has an accessible node in neck or axilla that seems signific or a mediastinal mass projecting well out into the lung field, or a parenc mal nodule of say more than 5 cm in diameter, and refuses node biopsy thoracotomy as the case may be, aspiration biopsy might be permitted. the hands of those familiar with that technic and with a pathologist av able willing to attempt diagnosis of material (smear and clot) obtained that method, a reasonably satisfactory working diagnosis may be possil

Treatment

Methods of treatment of thoracic malignant lymphoma are surgery, rac tion, chemotherapy, hormonal and supportive

Surgery is employed chiefly for biopsy of nodes or chest wall lesions. may be needed for exploration and biopsy of intrathoracic lymphomas, a may have occasional success in resecting completely or in large part a m diastinal lymphoma or a rare, apparently primary, pulmonary lymphom such as a lymphocytoma.

Radiation therapy remains the agent of greatest over-all usefulness *treating malignant lymphomas of the thorax* The preferred plan of trea ment of the superior caval syndrome in combination with nitrogen musta has already been described A similar plan may be used for the mediastin malignant lymphoma not causing severe pressure symptoms. Often in su cases the treatment of the mediastinum is combined with treatment of supr clavicular and cervical and perhaps axillary nodes.

Whether to give nitrogen mustard in full dose by a single injection or 2 to 4 fractions preceding the radiation therapy, is a matter for individual zation The choice depends on such factors as presence or absence of system symptoms, size of the lesions, state of the white cell and platelet count presence or absence of pregnancy in a woman patient, evidence of old c *active pulmonary tuberculosis*, severe myocardial disease, etc.

Spot treatment with x-rays with 250 kilovolts or 100 to 120 kilovolts, de

pending on the depth penetration desired, may be used for chest wall lesions such as those of ribs, vertebrae, breast or skin and subcutaneous tissues

Retreatment by radiation of previously irradiated fields may pose the problem of selection of supervoltage x-rays, the cobalt-60 beam, grid therapy or the betatron for x-rays or for the electron beam Interstitial irradiation by implantation permanently of gold radon seeds or temporary insertion of iridium needles or wires, has little if any practical or justifiable application in the lymphoma field, in the writer's opinion.

As previously mentioned, instillation into the pleural cavity of radioactive gold or phosphorus (or nitrogen mustard) for effusion may be of usefulness in some cases but by and large has not seemed as useful for malignant lymphomas as for other types of neoplasm

Radioactive isotopes such as phosphorus given orally or intravenously, have little or no place in the treatment of lymphosarcoma, Hodgkin's disease, mycosis fungoides or myeloma

Chemotherapy

A wide variety of chemotherapeutic agents is now available Intravenous injection of nitrogen mustard (HN2) or similarly acting polyfunctional alkylating agents such as Triethylene Melamine (TEM) is particularly indicated in patients with systemic symptoms or bulky or disseminated disease and is commonly followed by radiation therapy TEM usually causes less nausea and vomiting than does nitrogen mustard The commonly used doses are as follows nitrogen mustard 0 4 mg /Kg body weight in one dose or divided into 2 to 3 or 4 fractions; TEM 0 04 mg /Kg body weight daily for 3 days

For lymphomas disseminated more widely than to the chest, in ambulant patients with systemic symptoms, oral TEM in doses of 2 5 mg daily for 4 days or 5 mg daily for 3 days, may be followed on a maintenance basis by 2 5 to 5 mg once a week to a total of 30 to 40 mg The tablets should be taken on an empty stomach one hour before breakfast Caution should be exercised in cases of lymphocytic lymphosarcoma since they may prove to be sensitive, as patients with lymphatic leukemia often are, and therefore at first they should receive much smaller doses, say 2 5 mg. once followed by a wait of 10 days and a recheck of the white cell and platelet count before continuing with TEM

Leukeran (CB-1348, Chlorambucil) may be given in such cases in a dose orally of 0 2 mg /Kg body weight tapering to one-half that amount for maintenance or prolonged administration

These alkylating agents are all marrow depressants and the blood count, especially the white count and platelet count, must be watched at frequent intervals of 7 to 10 to 14 days

The allegation that nitrogen mustard can restore radiosensitivity to a

lymphoma that has become radioresistant, has never been documented to the writer's satisfaction.

The antimetabolites such as 6-Mercaptopurine and Methotrexate (Amethopterin) may be useful in some cases in which the lymphoma has become widely generalized or accompanied by a leukemic state In general they have been more useful for treatment of the malignant lymphomas of children than for cases in adults.

Particularly if one is treating bulky disease that is likely to have been growing rapidly or to be destroyed rapidly, hyperuricemia may become a danger and may have to be combatted by slowing the treatment and maintaining a large fluid intake and output. The value of administration of sodium bicarbonate for hyperuricemia is somewhat doubtful.

With or without detectable lesions of bones, hypercalcemia, with or without hyperuricemia may be a troublesome complication.

Hormonal Therapy

For some time before ACTH and the corticosteroids became available for clinical trial, there had been a few reasons to suspect that in some unknown manner the lymphomas might in part be causally associated with some disturbance of the endocrine system and perhaps modifiable by some hormonal alteration. Male sex preponderance, tendency for somewhat better prognosis for women with Hodgkin's disease during the period of active ovarian function, apparent onset of Hodgkin's disease or its worsening during or soon after pregnancy, unfavorable effect of androgen therapy, oft noted onset of some lymphosarcomas at about the menopausal time, onset following some severe emotional shock—such observations, subject to many exceptions, together with reports of Dougherty and White on lymphatic effect of corticosteroids, were among bits of evidence that suggested hormonal factors at play. Now that ACTH and corticosteroids have been so extensively employed, one almost wonders how we got along without them before. Like polyfunctional alkylating agents they have become almost indispensable in palliative care of advanced cases, although having failed completely to cure any of the lymphomas, and although fraught with risk of dangerous side effects.

When a malignant lymphoma in the chest becomes advanced, with few exceptions the disease is likely to be generalized with the patient in a generally deteriorated condition, often with pancytopenia This poor general state of marrow depression, frequently associated with fibrosis of the lung following previous irradiation, is often an unfortunate iatrogenic condition reflecting the unavoidable results of the far from satisfactory therapeutic measures that unfortunately are the best now available, namely radiation therapy and the alkylating agents, no matter how skillfully employed

It is in such situations particularly that one turns to the use of corticosteroids in hopes of increasing appetite and sense of well being, of perhaps

improving marrow function, of lessening pain, fever or itching, and perhaps of causing some regression of the lymphomatous deposits. Occasionally there occurs a striking remission of the lymphomatous lesions For example, multiple cutaneous nodules of reticulum cell sarcoma or lymphosarcoma may completely disappear after moderate doses of Prednisone in the order of 30 to 40 mg a day for an adult

SUMMARY

In summary it may be said that the chest, as far as malignant lymphomas are concerned, is merely one part of the human body that is a common site, initially or secondarily Their histologic varieties are the same in the chest as elsewhere For diagnosis the tissue offering proof may be available in the chest itself, or may more readily be obtainable elsewhere Treatment, be it surgical, radiologic, chemical, hormonal or supportive, is subject to the same general principles that apply when these diseases affect, as they often do, other parts of the body The special principles governing diagnosis and treatment of malignant lymphomas of the chest derive from its peculiar anatomic and physiologic features

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CHAPTER 14

Pleural Tumors

By HERBERT C. MAIER, M.D.

PRIMARY TUMORS OF THE PLEURA are relatively rare but present some interesting pathologic and clinical features. The true incidence of such growths is difficult to estimate accurately because there has been much diversity of opinion concerning which neoplasms should be considered to be of pleural origin. In this discussion only those tumors will be included which are thought to arise from cells of the various elements of the visceral, mediastinal, diaphragmatic and parietal pleura Neoplasms which merely protrude into the pleural cavity by pushing the pleura ahead of them, but which do not originate from elements of the pleura, are not regarded as pleural tumors A failure to make such a distinction has resulted in the literature on pleural neoplasms being confused by the inclusion of tumors which are obviously of mediastinal or chest wall origin. The differentiation of some malignant primary pleural neoplasms from metastatic involvement of pleura by pulmonary or other growths continues to present a problem unless a complete autopsy has been performed

PATHOLOGY

An analysis of the cases recorded in the literature as primary pleural tumors was made by Heiman in 1944 At that time a rather long list of various types of pleural tumors was collected A study of these publications, most of which consisted of single case reports, indicated that there was a marked diversity in the terminology employed Thus, it became evident that a compilation of the tumors based on the pathologic designations utilized might convey a distorted picture. However, a review of these earlier reported cases does serve as a background for our current concepts of these neoplasms

The confused state of the literature at that time is evidenced by the fact that over 30 different terms had been employed to designate various histologic types of pleural tumors Analysis of the reports indicated, however, that the majority of the tumors fell in one of two categories. The most important group of tumors were those which at that time were considered to be of connective tissue origin (fibromas and fibrosarcomas). The malignant mesotheliomas (also called endotheliomas) constituted the other group. Among the rarer types were the neoplasms of smooth muscle, nerve or fatty origin. Pleural tumors of blood vessel and lymphatic origin are extremely rare

Segregation of pleural tumors into two main clinical groups is helpful The *localized* neoplasm is a discrete mass of widely varying size which lies somewhat free in the pleural space and often may have only limited areas of attachment to either the visceral or parietal pleura, or both The *diffuse* pleural neoplasm, by contrast, usually involves large portions of the pleural cavity and not infrequently may encase the entire lung The localized tumor may be benign or malignant, but is more commonly benign The diffuse pleural tumor, on the other hand, is almost always malignant although extrathoracic metastases are often not demonstrable even at autopsy

Among the localized tumors in the pleural space, those assumed to be of connective tissue origin were reported most frequently These ranged from so-called benign fibromas to more cellular neoplasms which were considered to be sarcomas It was very apparent that difficulty was encountered in differentiating some of the benign from the malignant growths, moreover, some of the large neoplasms which were considered sarcomatous on the basis of microscopic features showed little clinical evidence of malignant behavior

One of the important articles on pleural tumors was published by Klemperer and Rabin in 1931 At that time the information about the behavior of the fibrous pleural tumors in tissue culture was not yet available It had already been demonstrated by Maximow, however, that there was a close resemblance between the cellular elements of some tumors and the loose connective tissue seen in the latter phases of embryonic life The conclusion seemed justified, therefore, that such tumors represented a neoplastic growth of embryonic connective tissue Klemperer and Rabin considered the various neoplasms which resembled tumors of connective tissue origin to arise from subserous layers of the pleura In this regard it is pertinent to call attention to the anatomic constituents of the normal pleura There is a tendency to think of only the mesothelial layer, whereas the visceral as well as the parietal pleura consist of connective tissue layers with elastic and collagen fibers with blood vessels, lymphatics and nerves The deepest layer of the visceral pleura over the lung is intimately associated with the underlying alveoli Thus, most of the connective tissue at the surface of the lung is a part of the pleura rather than a component of the pulmonary tissue The intersegmental connective tissue septa which divide the lung into segments are extensions of the pleural connective tissue

Controversy, as related to the localized pleural tumors, has centered chiefly around the question as to whether such tumors arose from the subpleural connective tissue, from the connective tissue layers of the pleura itself or from the mesothelial cells of the pleura The term "subpleural" would seem not to refer truly to any part of the pleura itself, but to tissues immediately subjacent to the deepest pleural layer Yet, it may be noted frequently in the literature that a pleural tumor is said to arise from the subpleural connective tissue It would seem most probable that the author

meant that the growth arose from subserous layers of the pleura itself if it was considered correctly to be a pleural tumor. In a consideration of the diffuse mesothelioma, confusion seems to have been largely related to the fact that such tumors presented a varied cellular appearance, usually showing both epithelial and connective tissue elements. The explanation of this finding now appears well documented and is a forceful argument for the viewpoint that such pleural tumors are truly of mesothelial origin. Murray and Stout demonstrated that pleural tumors consisting predominantly of fibroblasts could develop the characteristics of mesothelial cells in tissue culture. Thus it seems well established that a pleural tumor may present as a fibroma or fibrosarcoma and conceivably originate from either mesothelial cells or the subserous connective tissue of the pleura. When epithelial elements are mixed in with the connective tissue components, the evidence would point strongly toward a pleural (mesodermal) origin. If the tumor consisted only of fibrous elements, either the subserous connective tissue of the pleura, or the pleural mesothelium might be considered as the possible cellular origin of such a neoplasm In an attempt to differentiate between subpleural and pleural origins, the gross relationships of the tumor to the pleura and lung deserve consideration. In some instances, a fibrous tumor nodule may be in the pleural space, between the visceral and parietal pleura, with only some adhesions binding it to the two pleurae. The blood supply to such a predominantly intrapleural tumor may be partly from the parietal and partly from the visceral pleura, or almost entirely from one or the other. [illegible] that one is dealing [illegible] is less con[illegible] tissue capsule with a distinct pleural covering In these latter cases it is debatable whether the tumor is derived from either mesothelial cells or fibroblasts of the pleura or even from subpleural connective tissue.

When a pleural cavity is rather diffusely involved by neoplastic tissue, it may be quite difficult to decide whether one is dealing with a primary or secondary growth. Anaplastic carcinoma of the lung may present a particular problem. The principle reason for confusion between mesotheliomas of the pleura and secondary carcinomatous involvement of the pleura is due to the fact that the mesothelial tumors are characterized histologically by the formation of tubes lined by cells which resemble the tubular structures of carcinomatous glands. The prominence of such areas in the mesothelioma may vary widely In many of the benign fibrous growths such tubular structures [illegible] pear [illegible] mesothelioma such tubular structures may be readily evident [illegible] present features not seen in the ordinary fibrous tumor of connective tissue origin. The tubular structures are much more common in the malignant

diffuse mesothelioma, and this fact has led to the interpretation by some pathologists that such tumors might be of both epithelial and mesodermal derivation. The correct viewpoint would seem to be that the various types of cells seen in such malignant mesotheliomas are merely variants derived from multipotential mesodermal cells.

At the present time, it may not be possible for the pathologist to be certain whether a particular fibrous tumor, which is very cellular, is benign or malignant. In the past such tumors were often diagnosed as fibrosarcoma. More recently the term "fibrous mesothelioma" has been employed by many pathologists for localized tumors, both benign and malignant Incomplete removal of tumors which originally appeared to be benign may result in malignant behavior On the other hand, pleural effusion, sometimes even bloody, may be present and yet no evidence of malignant spread develop It is important for the clinician to bear these factors in mind in trying to determine the prognosis in an individual case

Clinical Findings

Age Incidence

The age incidence of pleural tumors is rather different from that of pulmonary neoplasms in that there is not the same tendency for the growths to occur chiefly in later adult life The diffuse malignant mesothelioma in particular may occur in childhood, early adult life, or at some later age In my own experience, malignant mesotheliomas of the pleura have been more common than primary malignant tumors of the lung in patients under 20 years of age, of course, primary cancer of the lung is very rare in this age group

The localized fibrous mesothelioma of the pleura is most commonly discovered in the 40 to 60 year age range Since some of these tumors may be slow growing and not produce symptoms until large size has been attained, these neoplasms may actually develop at a considerably earlier age period than the data suggests

Sex Distribution

The sex distribution of pleural tumors differs from that observed with primary neoplasms of the lung One does not find the marked preponderance of cases to be in males as is such a striking feature of bronchogenic carcinoma Moreover, if the pleural tumors are divided into subgroups, it may be found that some types of pleural neoplasms are more common among females The large growths without metastases which have been reported as cellular fibromas, fibrosarcomas and localized fibrous mesotheliomas apparently are more common in females There does not seem to be any pronounced sex predilection in the diffuse malignant mesotheliomas

meant that the growth arose from subserous layers of the pleura itself if it was considered correctly to be a pleural tumor. In a consideration of the diffuse mesothelioma, confusion seems to have been largely related to the fact that such tumors presented a varied cellular appearance, usually showing both epithelial and connective tissue elements. The explanation of this finding now appears well documented and is a forceful argument for the viewpoint that such pleural tumors are truly of mesothelial origin Murray and Stout demonstrated that pleural tumors consisting predominantly of fibroblasts could develop the characteristics of mesothelial cells in tissue culture. Thus it seems well established that a pleural tumor may present as a fibroma or fibrosarcoma and conceivably originate from either mesothelial cells or the subserous connective tissue of the pleura. When epithelial elements are mixed in with the connective tissue components, the evidence would point strongly toward a pleural (mesodermal) origin If the tumor consisted only of fibrous elements, either the subserous connective tissue of the pleura, or the pleural mesothelium might be considered as the possible cellular origin of such a neoplasm. In an attempt to differentiate between subpleural and pleural origins, the gross relationships of the tumor to the pleura and lung deserve consideration. In some instances, a fibrous tumor nodule may be in the pleural space, between the visceral and parietal pleura, with only some adhesions binding it to the two pleurae The blood supply to such a predominantly intrapleural tumor may be partly from the parietal and partly from the visceral pleura, or almost entirely from one or the other. Thus, in some cases the gross findings strongly suggest that one is dealing with a true pleural tumor. In other instances, the gross pathology is less conclusive in that the tumor presents as a mass with a connective tissue capsule with a distinct pleural covering In these latter cases it is debatable whether the tumor is derived from either mesothelial cells or fibroblasts of the pleura or even from subpleural connective tissue.

When a pleural cavity is rather diffusely involved by neoplastic tissue, it may be quite difficult to decide whether one is dealing with a primary or secondary growth Anaplastic carcinoma of the lung may present a particular problem. The principle reason for confusion between mesotheliomas of the pleura and secondary carcinomatous involvement of the pleura is due to the fact that the mesothelial tumors are characterized histologically by the formation of tubes lined by cells which resemble the tubular structures of carcinomatous glands. The prominence of such areas in the mesothelioma may vary widely. In many of the benign fibrous growths such tubular structures may not be evident and therefore the tumor may histologically appear as a fibroma or fibrosarcoma. In an occasional case of localized benign mesothelioma such tubular structures may be readily evident and clearly present features not seen in the ordinary fibrous tumor of connective tissue origin The tubular structures are much more common in the malignant

diffuse mesothelioma, and this fact has led to the interpretation by some pathologists that such tumors might be of both epithelial and mesodermal derivation The correct viewpoint would seem to be that the various types of cells seen in such malignant mesotheliomas are merely variants derived from multipotential mesodermal cells

At the present time, it may not be possible for the pathologist to be certain whether a particular fibrous tumor, which is very cellular, is benign or malignant In the past such tumors were often diagnosed as fibrosarcoma More recently the term "fibrous mesothelioma" has been employed by many pathologists for localized tumors, both benign and malignant. Incomplete removal of tumors which originally appeared to be benign may result in malignant behavior. On the other hand, pleural effusion, sometimes even bloody, may be present and yet no evidence of malignant spread develop It is important for the clinician to bear these factors in mind in trying to determine the prognosis in an individual case

Clinical Findings

Age Incidence

The age incidence of pleural tumors is rather different from that of pulmonary neoplasms in that there is not the same tendency for the growths to occur chiefly in later adult life The diffuse malignant mesothelioma in particular may occur in childhood, early adult life, or at some later age In my own experience, malignant mesotheliomas of the pleura have been more common than primary malignant tumors of the lung in patients under 20 years of age, of course, primary cancer of the lung is very rare in this age group.

The localized fibrous mesothelioma of the pleura is most commonly discovered in the 40 to 60 year age range Since some of these tumors may be slow growing and not produce symptoms until large size has been attained, these neoplasms may actually develop at a considerably earlier age period than the data suggests

Sex Distribution

The sex distribution of pleural tumors differs from that observed with primary neoplasms of the lung One does not find the marked preponderance of cases to be in males as is such a striking feature of bronchogenic carcinoma Moreover, if the pleural tumors are divided into subgroups, it may be found that some types of pleural neoplasms are more common among females. The large growths without metastases which have been reported as cellular fibromas, fibrosarcomas and localized fibrous mesotheliomas apparently are more common in females. There does not seem to be any pronounced sex predilection in the diffuse malignant mesotheliomas

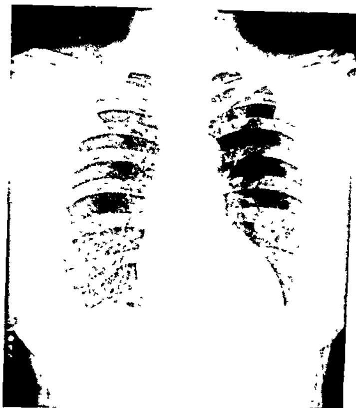


Fig 1—The small rounded density in the left lung field was shown on the lateral film to be adjacent to the chest wall posteriorly A limited surgical incision was made for this benign fibrous mesothelioma

Symptomatology

In some cases of pleural tumor, especially when the growth is small and benign, there may be no symptoms and the only evidence of a lesion may be the discovery of an abnormal shadow on the roentgenogram of the chest (fig 1). In other cases there may be a history of pain and swelling of various joints of months or even many years duration. At times, the arthralgia is accompanied by fever Often, such patients are treated for arthritis without the etiologic factor of the chest tumor being suspected or recognized. If clubbing of the fingers is present, as is usual in these cases of pulmonary osteoarthropathy, the physician should suspect the existence of some type of intrathoracic tumor or suppuration unless a congenital cardiac lesion is present Although pulmonary osteoarthropathy is more frequently seen with cancer of the lung than with pleural tumors, it occurs in an unusually high percentage of large fibrous mesotheliomas of the pleura.

Benign pleural tumors may attain considerable size and still not cause any symptoms Because of their peripheral location, these neoplasms rarely

cause bronchial symptoms, because airway compression is rare unless the pleural growth is large. When the tumor is of large size chest discomfort, dyspnea and cough may be present The cough is usually nonproductive Hemoptysis is rare in benign cases

Occasionally, fever and chilly sensations are noted in association with joint manifestations and pulmonary osteoarthropathy. Such findings should not be considered as indicating that the tumor is necessarily malignant, as this clinical feature is notable in some cases of apparently benign localized fibrous pleural mesothelioma

The symptomatology of patients with a malignant mesothelioma usually differs from that seen in the benign case This is particularly true if a diffuse mesothelioma is present Such patients may complain of weakness and chest pain, dyspnea may be prominent, and weight loss apparent In fact, in some cases, the course of the illness may be quite suggestive of an acute pleuritis or even empyema. Hemoptysis may be present

Roentgenographic Features

In a discussion of the roentgen findings in patients with a pleural tumor it is helpful to divide the cases into the localized and diffuse type, although some overlapping may occur The localized pleural mesothelioma may appear as a spherical or oval mass of density superimposed on the aerated lung field. The larger growths may show various irregular shapes The margins, which are usually quite clearly defined, may be slightly nodular The mass is usually of homogenous water density. The location of the mass may lead to a suspicion that the tumor may be of pleural origin because a study of the roentgenograms in various projections indicate that the mass is at the periphery of the lung or perhaps in the region of an interlobar fissure (fig. 2). It is not to be inferred by this statement, however, that the pleural tumor can be differentiated from a peripheral pulmonary carcinoma on the basis of roentgen features alone. The smallest tumor in our series was almost hidden behind a rib due to its small size Some benign mesotheliomas may be large enough to fill a large part of the hemithorax and even cause mediastinal displacement

When the mass arises in the long fissure, its position, and particularly its ovoid shape with the long axis in the direction of the fissure as seen in the lateral roentgenogram, may suggest a pleural tumor (fig 3) When the tumor is located in the basal portion of the thorax, the shadow of the growth may merge with that of the diaphragm and it may be misinterpreted as an elevated diaphragm

A pleural lipoma may present a bizarre roentgen appearance Instead of being a round or oval mass, it may project from the pleura as a number of irregular, finger-like masses which appear as a shadow of unusual contour and varying density



Fig 2—(A and B) Malignant mesothelioma in a 33 year old man Lesion inoperable Treated by radiotherapy



Fig 3—(A and B) Twelve year old boy Note large area of density along course of long fissure Diagnosis of a malignant neoplasm was established by needle aspiration A pleuro-pneumonectomy was performed for this malignant mesothelioma Death from recurrent disease in 2 years

Diagnostic Procedures

As previously mentioned, some of the more diffuse and malignant mesotheliomas of the pleura may simulate a localized or even fairly diffuse pleura effusion both on clinical and roentgenographic grounds. Therefore, a thora-

centesis is frequently employed as a diagnostic procedure in this particular group of cases If only a small amount of material which appears to be blood is obtained by such a diagnostic needling, the tap may be erroneously considered to have been traumatic and the "blood" discarded Yet, if such "blood" were sent to the laboratory, proper microscopic examination would often demonstrate the presence of malignant tumor cells and hence establish the diagnosis

Bronchoscopic examination may occasionally reveal bronchial distortion, due to extrinsic pressure from a pleural tumor which encroaches on the hilar portion of the lung. Usually, however, bronchoscopic examination is negative Cytologic studies of the bronchial secretions would only be positive when a malignant mesothelioma has invaded the lung

Treatment

The treatment advised for pleural tumors will be influenced by the pathologic characteristics of the particular tumor encountered. Surgical excision is indicated for the localized benign lesion such as fibroma, lipoma and mesothelioma. In such cases, a positive preoperative diagnosis is rarely established, thoracotomy is undertaken for the removal of an intrathoracic mass of uncertain nature Removal of a localized pleural tumor which has only a small area of attachment to the lung or parietal pleura may be a relatively simple procedure Usually, little pulmonary tissue needs to be excised in such a case This is in marked contrast to the situation encountered in the case of the diffuse tumors Many of the diffuse mesotheliomas are inoperable or can only be removed by the procedure of pleuropneumonectomy Such malignant mesotheliomas can rarely be excised without contamination of the pleural space with neoplastic cells Postoperative radiation therapy is indicated in such cases

Following surgical removal of a localized fibrous mesothelioma of the pleura from a patient with the joint manifestations of pulmonary osteoarthropathy, an immediate dramatic disappearance of the joint pain and swelling is to be anticipated postoperatively

Hyaline Pleural Plaques

Although these firm whitish plaques which are occasionally seen in the parietal and diaphragmatic pleura are not neoplasms, a brief mention of this lesion seems warranted in a discussion of pleural tumors Grossly, these can be confused with the metastatic implants in the pleura The appearance is that of an area of elevation and thickening of the pleura of varying size with sharp borders The surface of the plaque is whitish, smooth and shiny without visceroparietal pleural adhesions in that area The plaque tends to be of rather uniform thickness (a few millimeters) which should readily

are not always painful. Unless it is restricted to the skin or breast, a tumor of the thoracic wall is usually not mobile. It may be hard or soft, symmetric or nodular With continued growth cutaneous ulceration may result. A pulsating tumor is considered diagnostic of metastasis from cancer of the thyroid or hypernephroma.[7] Rarely, the presenting symptoms are pulmonary, i e., cough, dyspnea and pleural effusion. Sometimes, the tumor is diagnosed only after pathologic fracture.

Diagnosis

The diagnosis of tumors of the thoracic wall can be difficult and is usually made by roentgenography and biopsy. Obviously, this does not imply that a careful history and physical examination together with indicated laboratory procedures are not valuable The history may reveal the duration and progression of symptoms and a preceding injury or treatment for previous malignant disease The physical examination may show evidence of infection, a systemic disease or a primary lesion elsewhere. Laboratory studies should include the white blood cell count, urinalysis for cells and protein, serologic tests for syphilis and selected special procedures, such as determination of serum phosphorus and calcium, acid and alkaline phosphatase, and uric acid, and intradermal antigenic and complement fixation tests.

Roentgenography is particularly valuable in the diagnosis of osseous lesions In addition to the usual postero-anterior, lateral and oblique views, planigrams are sometimes useful in localizing tumors, and pneumothorax can be used to separate the lung from a tumor of the thoracic wall that protrudes intrathoracically The roentgenogram should be taken to delineate bone detail, except when it is desired to study the soft tissues specifically. Normal results of roentgenography, however, do not rule out the diagnosis of a tumor, even an osseous neoplasm By intraosseous phlebography,[24] an osseous lesion may be demonstrated when the result of roentgenography is questionable.

Biopsy is usually necessary to make the diagnosis If the tumor is small (up to a few centimeters or occupying one rib only), it should be surgically excised If it is large and ulcerating or fungating, biopsy is probably best performed with an endothermic loop with bipolar coagulating current. For large deep lesions, needle biopsy is most practical but selection of treatment should not be influenced by a negative result. Needle biopsy is also useful in the diagnosis of a small bony tumor that is strongly suspected of being metastatic.

Differential Diagnosis

In the differential diagnosis of neoplasms of the thoracic wall one must primarily consider the conditions that may simulate these lesions (table 5).

Obviously, neoplasms of the thoracic wall may themselves simulate other conditions, and it is well to recognize this fact, but it is not within the limits of this discussion to consider the many causes for the type of symptoms associated with neoplasms of the thoracic wall In fact, the conditions that can be mistaken for lesions of the thoracic wall will merely be mentioned here Some of these are confusing only in a clinical sense and others (as indicated by the asterisk in table 5) from the roentgenographic standpoint.

Even normal anatomic relationships may be mistaken for tumors of the thoracic wall Roentgenographic misinterpretation of the breast or nipple is possible after mastectomy or when one side of the chest is pressed more firmly against the cassette In children the centers of bone ossification may cause confusion A prominent anteflexed but otherwise normal xiphoid has been resected as a bone tumor[31]

The prominent hypertrophied costal cartilage is probably the most frequent condition for which a physician is asked to rule out a diagnosis of neoplasm of the thoracic wall, but other congenital anomalies of bone (i e, pigeon breast) and soft tissues (i e, polymastia, polythelia) may be clinically confusing Rib anomalies (bifid fused ribs, etc) and infantile cortical hyperostosis may be problems from the radiologic or clinical standpoint. In the latter condition there may be tenderness and swelling over the scapula, ribs or a clavicle with a roentgenographic appearance that can be mistaken for osteogenic sarcoma It usually produces multiple lesions, however, and occurs during the first year of life

The post-traumatic conditions listed in table 5 will appear primarily as masses with varying degrees of tenderness The history of trauma may be of little help in the differential diagnosis, since it is so common in primary neoplasms of the thoracic wall Muscle rupture is most likely to occur in the trapezius muscle Myositis ossificans deserves special consideration, since it not only can resemble a sarcoma from the clinical and radiologic standpoint but may possibly undergo malignant change[36] In the days before the recoilless rifle it was a more common finding in the thoracic wall than at present, for it used to be known among the infantrymen as "drill bone" or "exercise bone," the result of injury to the pectoralis muscle by the impact of the discharging musket

Infections may simulate tumors, granulomatous or ulcerative lesions of the soft tissues of the thoracic wall or inflammatory lesions of the bones. They may not be easily differentiated from primary neoplasms without biopsy or culture The infectious diseases of greatest importance in the differential diagnosis of neoplasms of the thoracic wall are those produced by pyogenic bacteria, tuberculosis, actinomycosis, blastomycosis, syphilis and brucellosis. The presence or absence of a systemic septic response is not always helpful in differential diagnosis, since this may be present with some

neoplasms, notably Ewing's tumor, or may be masked in an antibiotic-treated infection. It is important to think of arthritis, particularly gout, in any painful swelling of the articulations.

Of the circulatory conditions that may simulate neoplasms of the thoracic wall, the aneurysmal bone cyst and the phantom bone (spontaneous absorption of bone) may actually be benign tumors of a hemangiomatous nature The aneurysmal bone cyst is most common in the vertebrae of adolescents. Slowly progressing pain and swelling are the usual symptoms The characteristic roentgenographic features have been described as a "subperiosteal blowout"[19] in which there is an eccentric, ballooned out distention of the periosteum into the soft tissues, surrounded by a thin layer of cortex or periosteal new bone. Trabeculae are present in the rarefied area, being coarse at the periphery and more delicate toward the center. Recommended treatment is excision or curettage with irradiation for those in inaccessible regions. Without treatment, progressive local destruction will occur. Even with incomplete treatment the tumor has been known to regress

Spontaneous absorption of bone is a rare condition but most cases have involved the thoracic wall, often with massive destruction of a large area [8, 11, 43]

Of the metabolic disturbances that must be differentiated from neoplastic disease of the thoracic wall, lipid reticuloendotheliosis is the most important. Bony defects, usually multiple, may be seen in all three variations of this disease The most important entity, however, is the eosinophilic granuloma which represents the disease as it occurs in the older children and adults It is most common in men. There is a sudden onset of pain, swelling and tenderness The radiologic picture shows sharply defined, rounded or scalloped translucencies centrally placed in the bone (frequently the ribs and scapulae) which may be expanded by it. It responds favorably to irradiation in moderate dosage, but lesions may heal spontaneously.

Of the remaining conditions listed in table 5 brief comment should be made about fibrous dysplasia of bone and Tietze's syndrome The former is a common condition occurring with greatest frequency in the ribs Although it is usually polyostotic, monostotic lesions are not rare It affects primarily young people and is usually asymptomatic, the lesions being discovered on roentgenography of the chest. Rarely is there a systemic form of the disease with cutaneous and endocrine changes known as "Albright's syndrome." Well defined zones of rarefaction, which are multilocular or trabeculated in appearance, are demonstrated roentgenographically. The lesions develop slowly and are said to stop growing at puberty. If lesions are multiple, the patient should be kept under observation and treated only if there is evidence of malignant change; single lesions should be excised.

Tietze's syndrome may not actually exist as an entity but it has been de-

scribed as "painful, nonsuppurative swelling of the sternoclavicular or costochondral joints."[22] The second costochondral junction is the most frequently involved Pain is dull and aching, and accentuated by deep breathing and coughing It persists for weeks or months but there is no permanent disability. The swelling is minimal and there are no signs of inflammation. There are no roentgenographic or laboratory abnormalities. Treatment is symptomatic.

Treatment

Management of tumors of the thoracic wall depends on various factors (1) histogenesis, (2) growth propensity, (3) location, (4) extent of involvement, (5) fixation, (6) regional or distal metastases, (7) primary or recurrent status, (8) sensitivity to irradiation and (9) patient's general physical status (particularly respiratory and cardiac) in relation to extent of surgical excision required for cure The initial objective should be determination of the histologic type of the tumor Only in rare instances in which the clinical picture strongly suggests a benign lesion should biopsy not be done However, if the question of a neoplasm exists, the patient must be kept under close observation Whereas not all benign soft tissue neoplasms require treatment, it is preferable to remove all accessible lesions to prevent continued growth or malignant transformation Observation without biopsy is not recommended for the "benign" bony lesions unless they are multiple because one can never be sure a bone lesion is not malignant However, benignancy is suggested by the quiescent existence of the tumor for many years without change or the roentgenographic appearance of circumscription and expansion without destruction of the bone On the other hand, a malignant tumor is suggested by the sudden onset of pain, rapid growth and roentgenographic evidence of an illdefined, destructive lesion that perforates the cortex or transgresses the periosteum to form an associated soft tissue tumor Also, it is more likely to be present when adjacent or multiple bones are involved, and when the tumor is in the sternum

Surgical excision and roentgenotherapy are the usual methods of treatment of tumors of the thoracic wall Endocrine therapy is extremely valuable in the management of mammary cancer, and metastatic carcinoma of the prostate Chemotherapy is of limited usefulness in neoplasms of the thoracic wall, and perfusion is impractical Therapeutic irradiation or surgical excision should be preceded by biopsy In fact, at the time of biopsy the surgeon should be prepared to perform definitive surgical treatment if this seems necessary.

The most useful application of irradiation is in the palliative treatment of metastasis to the bones In this regard, success is sometimes achieved in tumors ordinarily considered to be radioresistant. Reticulum cell sarcoma

is the primary malignant lesion that responds most favorably to irradiation. Ewing's sarcoma and myeloma are also radiosensitive. However, localized tumors, even though radiosensitive, are sometimes more easily excised. In general, irradiation should be employed only if (1) consent for operation is refused, (2) the tumor is in a surgically inaccessible area or (3) is not resectable. Fractional roentgenotherapy has been able to retard the growth and reduce the bulk of nonoperable tumors so that they become resectable.[38] Several cases have been reported of malignant tumors developing at the site of irradiation of bone.[5]

The principles of surgical treatment are essentially the same as for tumors elsewhere in the body. Resection should be done, although in certain areas (i.e., body of the vertebra) this may not be feasible. Excision with a wide margin of surrounding, uninvolved tissue is necessary for malignant tumors. Sarcomas frequently are pseudoencapsulated and one must avoid the temptation to enucleate them. It should be remembered that depth of excision is as important as width. For tumors arising in or invading the skeletal cage, it is necessary to resect the bones, and underlying pleura in the case of the ribs. In the treatment of malignant tumors, the entire rib must be removed because of the great propensity for intramarrow[45] and periosteal[15] extension. In primary tumors portions of 2 adjacent ribs should be removed as well. Lesions of the clavicle should also be totally resected. If the tumor is at the lower end of the sternum and scapula, however, the upper portions may be preserved. Obviously, with tumors of the vertebra, resection is possible only when the spinous or transverse processes are involved. For lesions of the body of the vertebra, the only feasible surgical procedure is curettage. It must be realized that the bulk of a tumor of the thoracic wall may extend intrathoracically. In such cases, the pleural space should be entered about two interspaces away from the obvious tumor in order to evaluate this extension. If it is involved, one should not hesitate to resect portions of the diaphragm, pericardium or lung. Although many tumors of the thoracic wall do not metastasize via the lymphatic system, resection of regional lymph nodes should, if possible, be done in those that do (those of epithelial origin, rhabdomyosarcomas, malignant synoviomas and spindle cell sarcomas of undetermined histogenesis).

Except for excision of tumors of the external soft tissues, resection of the thoracic wall was not safe until introduction of positive pressure anesthesia just before the turn of the century. Parham,[39] who published in 1899 the first review of tumors of the thoracic wall, quoted Dieffenbach as saying that "the like operations go too much counter to all physiology and give to the beautiful saving art the appearance of cruel annihilation-mechanics." However, at present, extensive resections can be accomplished without sudden pulmonary collapse and shock. The problems of the resultant paradoxic

motion of the thoracic wall (inadequate ventilation, poor cough mechanism and clearing of secretions) can be temporarily controlled with tracheostomy or obviated by various thoracoplastic procedures using fascial or prosthetic grafts, osteoperiosteal flaps, skin (including breast) and muscle flaps However, there is little functional or cosmetic disturbance from removal of one or two ribs, the sternum, clavicle or even the scapula Large bony defects are well tolerated in the upper portion of the posterior aspect of the chest because of the thick musculature here. Whenever the upper portion of the sternum is removed, McManus and associates[28] recommended excision of the medial halves of the clavicles also since removal of the support of the clavicle allows it to compress the neurovascular bundle The only indication for interscapulothoracic amputation of the arm is an extensive malignant tumor of the scapular region with involvement of the shoulder joint

Prognosis

Many factors influence the prognosis of tumors of the thoracic wall, the most important being the growth propensity of the neoplasm As a rule, however, these tumors have a poorer prognosis than the same types occurring elsewhere, particularly the extremities

Tumors of Soft Somatic Tissues

Soft tissue neoplasms may occur anywhere on the thoracic wall (table 2). In collected series often anterior lesions are not differentiated from posterior ones In fact, tumors of the posterior thoracic wall are frequently included with those occurring on the "back" Also, many neoplasms have been designated as histologically undifferentiated, providing a heterogenous group which defies accurate description The following discussion is based on tumors of known histogenesis

Epithelial tumors (table 1) are essentially tumors of the skin and breast They will not be considered in this discussion

Fibrous Tumors

Of the fibrous tumors (table 1) only the fibrosarcoma, which is the most important malignant tumor, will be considered here. It occurs in young adults, frequently in the region of the shoulder, as a deeply fixed, firm, painless nodule which only secondarily invades and ulcerates the skin Blood-borne metastasis (lungs) is common but lymph node metastasis occasionally occurs Treatment is radical surgical excision, with removal of the regional lymph nodes if palpable or when the tumor is in close proximity to them. It is not considered to be a radiosensitive tumor, but because irradiation induces some shrinkage and reduction in growth activity, it can be used palliatively for an otherwise nonresectable tumor. Solitary pulmo-

TABLE 1—*Soft Tissue Tumors of the Thoracic Wall*

Type of Tissue	Benign	Malignant
Epithelial		
Epidermal		
	Verruca (Wart)	
	Seborrheic keratosis	
	Senile keratosis	Squamous cell carcinoma
		Bowen's disease
		Basal cell carcinoma —superficial basal cell c cinoma
	Melanocytic nevi	Malignant melanoma
	Intradermal	Juvenile melanoma
	Junctional	
	Compound	
	Blue nevus (*Jodassahn-Tieuche*)	*Malignant blue nevus*
	Keratinous cyst	
	Sebaceous cyst	
	Steatocystoma multiplex	
	Dermoid cyst	
Adenexal		
Breast	Intraductal papilloma	Adenocarcinoma
		Scirrhous
		Medullary
		Comedo
	Fibroadenoma	
	Intracanalicular	Cystosarcoma Phyllodes
	Pericanalicular	Paget's disease
Other	Adenoma	Carcinoma of sebaceous, apo crine or eccrine gland
	Sebaceous epithelioma	
(Sebaceous, apocrine and eccrine glands *and hair*)	Apocrine	
	Syringoma	
	Cylindroma	
	Myo-epithelioma	
	Tricoepithelioma	
	Calcifying epithelioma (Mal-*hebre*)	
	Hidroadenoma papilliferum	
Fibrous	Fibroma	Fibrosarcoma
	Keloid	
	Desmoid	
	Dermatofibroma (Histocytoma)	Dermatofibrosarcoma protuberans
Adipose	Lipoma	Liposarcoma
	Lipomatosis	
	Hibernoma	Malignant hibernoma
Muscle	Leiomyoma	Leiomyosarcoma
Smooth	*Rhabdomyoma*	Rhabdomyosarcoma
Striated	Granular cell myoblastoma	Malignant granular cell myoblastoma

TABLE 1—*Continued*

Type of Tissue	Benign	Malignant
Vascular	Hemangioma Capillary Hypertrophic Cavernous Pyrogenic granuloma Lymphangioma Capillary Cavernous Cystic hygroma Glomous tumor	Metastasizing angioma Angiosarcoma Kaposi's hemorrhagic sarcoma Angioendothelioma Hemangiopericytoma Granulation cell sarcoma Lymphangiosarcoma
Reticulo endothelial		Reticulum cell sarcoma Stem cell lymphoma Clasmatocytic lymphoma Lymphosarcoma Lymphoblastic lymphoma Lymphocytic " Follicular lymphoma Hodgkin's disease Myocosis fungoides
Peripheral Nerve	Neurilemmoma (Schwanoma) Neurilemoblastoma (Neurofibroma) Neurofibromatosis Neuroma Ganglioneuroma	Malignant neurilemmoma
Synovial	Benign synovioma Giant cell tumor of tendon (xanthoma)	Synovial sarcoma
Undifferentiated	Myxoma Mesenchymoma	Myxosarcoma Malignant mesenchymoma
Heterotopic bone and cartilage	Osteoma Chondroma	Osteogenic sarcoma Chondrosarcoma

nary metastasis does not preclude radical treatment since associated pulmonary resection may be curative

Adipose Tumors

Lipomas are undoubtedly the most common fatty tumors in the thoracic wall They usually occur in the subcutaneous tissue of middle-aged women but sometimes in the intermuscular planes Lipomas transilluminate whereas neurofibromas do not They appear as circumscribed radiolucent areas on soft tissue roentgenograms With increasing size, they can produce pressure; therefore, large lipomas should be exised Local recurrence is possible if all pseudopodia are not removed Malignant transformation is rare, probably only in extremely bulky tumors Most liposarcomas are believed

of cavernous lymphangiomas is the shoulder, and the cystic hygroma is not infrequently seen in the thoracic wall, particularly the axillary region. Lymphangiomatous tumors are radioresistant and require excision.

Although most frequent on the finger tips (in women) or forearms and knee (in men), glomus tumors (table 2) have been reported in the thoracic wall.[41] They are radioresistant and require excision.

Reticuloendothelial Tumors

Malignant lymphomas (table 1) are multiple, 40 per cent of patients initially seen with solitary lesions eventually having generalized disease. Leukemia develops in some, particularly in the lymphosarcoma group. Of the 618 malignant lymphomas reviewed by Gall and Mallory,[13] only 70 were localized Only one of these was definitely in the thoracic wall (but in a bone) but another was reported in the "back." Although most malignant lymphomas are radiosensitive, excision is probably the best treatment for localized lesions.

Neurogenic tumors may arise from the nerve sheath (neurilemmoma, *neurilemmoblastoma) or the nerve fiber (neuroma, ganglioneuroma). In* the thoracic wall intercostal nerves are usually involved, the most frequent location of the tumor being the lateral aspect of the chest and the least frequent the anterior thoracic wall [17] A tumor arising from the brachial plexus may be discovered on the thoracic wall, however! Neurogenic tumors can attain a large size without producing symptoms, particularly if they protrude intrathoracically, where the only roentgenographic abnormality may be a soft tissue density, perhaps with erosion of the rib or vertebral body.

Benign tumors are much more common than malignant ones and at least 80 per cent are neurofibromas [17] *Malignant transformation occurs only with* neurofibromas and ganglioneuromas According to Pack and Ariel,[25] it de*velops in 10 per cent of patients* with neurofibromatosis, but is generally of low grade in contrast to neurogenic sarcomas which arise *de novo* [33] Single tumors should be excised, the intercostal nerves can be sacrificed without disability. Excision is recommended for multiple tumors only when cosmetically desirable or when the lesion becomes complicated (traumatized, infected or growing). Patients with neurofibromatosis *should be kept* under observation, however, especially during pregnancy when changes are prone to occur There is some *question whether neurogenic sarcoma* ever exists as an entity separate from fibrosarcoma [44] These tumors usually occur *in young adults* They are radioresistant and require radical excision for cure Rib resection should be done when an intercostal nerve is involved. The prognosis is favorable with this treatment.

Synovial Tumors

That these tumors rarely occur in the thoracic wall is not surprising when one considers the relatively small amount of synovium (the joints of the

TABLE 2—*Relative Incidence of Chest Wall Involvement (Soft Tissue Neoplasms)*

Author	No of Cases	Most Frequent Site	No	Chest No	Ant Chest	Post Chest
		Malignant Melanoma				
Webster et al (1944) *Columbia University*	162	Lower extremities	51	13	8	5
Ackermann (1949) Barnes Hospital	185	Lower extremities	68	25		
		Desmoid				
Pearman and Mayo (1942) Mayo Clinic	77	Anterior abdominal wall	55	10	6	4
		Fibrosarcoma				
Warren and Sommer (1936) Harvard University	136	Leg	41	12	5	7
Gentele (1951) Radiumhemmet	90	Leg	21	13	6	7
Pack and Ariel (1952) *Memorial Hospital*	39	Arm	15	9	2	7
		Dermatofibrosarcoma Protuberans				
Hertzler (1926) ?	22	Inguinal region	11	3		
Pack and Tabah (1951) Memorial Hospital	39	Trunk	29	14	8	6
Gentele (1951) Radiumhemmet	38	*Abdomen*	*11*	*9*	*7*	*2*
		Lipoma				
Adair et al (1932) Memorial Hospital	352	Forearm	40	94	39	55
		Liposarcoma				
Pack and Pierson (1954) Memorial Hospital	105 (non visceral)	Thigh	42	19	9	10
		Leiomyoma				
Stout (1937) Literature	80	Leg	32	16	13	3
Stout (1937) Columbia University	15	Leg	6	1	1	0

TABLE 2—*Continued*

Author	No of Cases	Most Frequent Site	No	Chest No	Ant. Chest	Post. Chest
		Rhabdomyosarcoma				
Pack and Eberhart (1952) *Memorial Hospital*	100	Thigh	41	11	6	5
		Hemangioma				
Shallow et al (1944) Literature	335	*Gastrocnemius*	31	40	17	23
Elkin and Cooper (1947) Emory University	19	Head	6	3		
		Angiosarcoma				
McCarthy and Pack (1950) Memorial Hospital	20	Leg	7	2	2	0
		Hemangiopericytoma				
Stout (1949) Collected	25	Leg	6	1	0	1
McCormack and Gallivan (1954) Cleveland Hospital	14	Lumbar region Thigh	2 2	4		
		Glomus Tumor				
Beaton and Davis (1941) Literature	271	Female-fingers Male forearm	116 39	1	1	0
Riveros and Pack (1951) Memorial Hospital	20	Fingers	7	2	1	1
		Benign Neurilemmoma				
Geschickter (1935) Johns Hopkins Hospital	70 (skin)	Head and neck	18	11	3	8
Pack and Ariel (1958) Memorial Hospital	63	Neck	21	5	4	1
		Malignant Neurilemmoma				
Vieta and Pack (1951) *Memorial Hospital*	31	Neck Anterior surface Forearm	7 7	2	1	1
		Synovial Sarcoma				
Pack and Ariel (1950) Memorial Hospital	60	Knee	13	3	1	2

thoracic wall are not freely movable) and tendon sheaths (the only true tendon in the thoracic wall belongs to the pectoralis minor muscle where it inserts into the coracoid process of the scapula) However, there is a report of a giant cell tumor of the tendon sheath[2] and several synovial sarcomas[12, 13] have been described These tumors were not in the region of joints, although they may have arisen from bursae, and support the opinion of Haagensen and Stout[14] that synovial sarcomas do not arise from living cells of joints, bursae and tendon sheath, but may come from mesenchymal tissue as suggested by Eisenberg and Horn [12] Synovial sarcomas have shown variable radiosensitivity Although generally considered to be radioresistant, cure by irradiation alone has been reported [34] However, wide surgical excision is the treatment of choice Regional lymph node resection is indicated, because although the tumor metastasizes primarily via the blood stream, it also spreads to the lymphatic system in a higher incidence than any other sarcoma

Mesenchymal Tumors

There are two groups of tumors of primitive mesenchyme (1) myxomas, which reproduce the characteristics of primitive mesenchyme and (2) mesenchymomas, which develop the diverse growth potentialities of the prodromal structural cell Myxomas are uncommon but have been seen in the thoracic wall (especially the breast) and should be widely resected because of their strong tendency to infiltrate with pseudopodia Stout[44] questioned whether the term, myxosarcoma, should be used, since these tumors do not metastasize, but they can cause death by invading contiguous organs Mesenchymomas are extremely rare but at least one case has been reported in the thoracic wall [37] These tumors are usually malignant and highly invasive Radical excision is indicated

Heteroptic Bone or Cartilage Tumors

These extraskeletal tumors probably arise also from primitive mesenchyme Several examples have been reported in the thoracic wall Such tumors must be differentiated from myositis ossificans and from periosteal sarcoma The tumors in this group are less malignant than their counterparts in the skeletal system but radical excision is indicated.

TUMORS OF BONE AND CARTILAGE

Neoplasms of the skeletal cage of the thoracic wall (table 3) are less common than those of the soft tissues, although 10 per cent of bone tumors occur in the ribs If one excludes metastatic tumors and myelomas, they are relatively uncommon They are twice as common in males as in females in contrast to soft tissue neoplasms which, because of breast tumors, are

Table 3—*Tumors of Bone and Cartilage*

Type of Tissue	Benign	Malignant
Hematopoietic		Myeloma (plasmocytoma) Multiple myeloma Primary malignant lymphomas of bone Reticulum cell sarcoma Lymphatic lymphoma Hodgkin's malignant lymphoma
Cartilaginous	Osteochondroma *Multiple exostoses* Chondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma *Primary* Secondary
Osseous	*Osteoma* Osteoid osteoma Osteoblastoma	Osteogenic sarcoma Parosteal osteogenic sarcoma
Unknown origin	Simple bone cyst *Giant cell tumor (osteoclastoma)*	Ewing's tumor *Malignant giant cell tumor* Adamantinoma
Fibrous	Nonosteogenic fibroma	Fibrosarcoma
Vascular	Hemangioma	Malignant angioma Angiosarcoma Angioendothelioma
Adipose	Lipoma *Central* Periosteal Secondary lipomatosis	Liposarcoma
Nerve	Neurilemmoma	
Notochord		Chordoma
Undifferentiated mesenchyme	Myxoma	

much more common in females The tumors have been found in all bones of the thoracic wall (table 4) most frequently in the ribs and least in the sternum At least 75 per cent of these tumors are malignant. Almost all tumors of the sternum are malignant. In the relatively inaccessible thoracic vertebrae, if metastatic tumors and myelomas are excluded, fortunately tumors are usually benign.

The most common primary tumor of the thoracic wall is the myeloma In operative series, however, the most common tumors are cartilaginous except those in the vertebrae, which are usually giant cell tumors.

Hematopoietic Tumors

Multiple myeloma is the most common neoplasm of bone. In general, a solitary plasma cell myeloma (plasmocytoma) is believed to be the same

disease but localized. Multiple myelomas are frequently seen in the skeleton of the thoracic wall (table 4) and often appear as a solitary lesion but seldom remain so Myeloma of bone occurs predominantly in older men and is rarely seen in patients younger than 30 years of age Progressive localized

TABLE 4—*Relative Incidence of Chest Wall Involvement (Bone and Cartilage)*

Author	No of Cases	Most Frequent Site	No	Chest No	Ribs	Sternum	Clavicle	Scapula	T Vert
"Solitary" Myeloma									
Pasternack and Waugh (1939) Literature	31	Femur	9	4	0	0	1	0	3
Bayrd and Heck (1947) Mayo Clinic	10	Vertebra	4	4	0	0	1	1	2
Carson et al (1955) Washington Univ , St Louis, Mo	18	Vertebra	9	1+	1	0	0	0	9 in ? vert
Multiple Myeloma									
Geschickter and Copeland (1949) Johns Hopkins Hospital	86	Vertebra *Rib*	15 *15*	31+	15	7	7	2	15 in ? vert
Carson et al (1955) Washington Univ , St Louis, Mo	78	Vertebra	52	61+	35	5	11	10	52 in ? vert
Dahlin (1957) Mayo Clinic	140	Vertebra	47	32+	17	5	8	2	47 in ? vert
Reticulum Cell Sarcoma									
Parker and Jackson (1939) Bone Sarcoma Registry	17	Femur	5	5	0	0	4	1	0
Francis et al (1954) Memorial Hospital	44	Femur	11	8+	2	2	0	4	2 in ? vert
Dahlin (1957) Mayo Clinic	70	Femur	18	9+	4	0	0	5	6 in ? vert
Osteochondroma									
Geschickter and Copeland (1949) Johns Hopkins Hospital	318	Femur	87	14	1	1	2	9	1
Dahlin (1957) *Mayo Clinic*	272	Femur	79	35	9	0	3	22	1
Chondroma									
Coley (1949) Memorial Hospital	24	Hand	11	1	1	0	0	0	0
Geschickter and Copeland (1949) Johns Hopkins Hospital	113	Hand	49	22	12	6	2	1	1
Dahlin (1957) Mayo Clinic	99	Hand	56	6+	3	0	0	3	4 in ? vert

TABLE 4—*Continued*

Author	No of Cases	Most Frequent Site	No	Chest No	Ribs	Sternum	Clavicle	Scapula	T Vert
Chondroblastoma									
Geschickter and Copeland (1949) Johns Hopkins Hosp	26	Femur	8	1	0	9	9	1	0
Dahlin (1957) Mayo Clinic	18	Femur	7	4	2	0	0	2	0
Dahlin (1957) Literature	61	Femur	25	2	0	0	0	2	0
Chondrosarcoma									
Geschickter and Copeland (1949) Johns Hopkins Hosp	121 (primary)	Femur	40	8+	1	0	1	6	2 in ? vert
Geschickter and Copeland (1949) Johns Hopkins Hosp	35 (Secondary)	Femur	13	3+	0	0	0	3	1 in ? vert
O'Neal and Ackerman (1952) Washington University, St Louis, Mo	40	Femur	6	11	10	0	0	1	0
Dahlin (1957) Mayo Clinic	218	Ilium	58	71	47	1	4	13	6
Osteoid Osteoma									
Jaffe and Lichtenstein (1940) Hospital of Joint Disease, New York	33	Tibia	8	0+	0	0	0	0	3 in ? vert
Sherman (1947) University of Chicago	30	Femur	7	0+	0	0	0	0	7 in ? vert
Dahlin (1957) Mayo Clinic	57	Vertebra Femur	7 23	2	0	0	0	2	0
Benign Osteoblastoma									
Lichtenstein (1956) Wadsworth General Hospital, Los Angeles	11	Vertebral column	4	1	0	0	0	0	1
Dahlin (1957) Mayo Clinic	17	Vertebral column, sacrum	8	3	0	0	0	0	3
Osteogenic Sarcoma									
Coley (1949) Memorial Hospital	283	About knee	129	31	14	3	2	10	2
Geschickter and Copeland (1949) Johns Hopkins Hosp	187 (osteogenic)	Femur	75	6	2	0	0	2	1
Geschickter and Copeland (1949) Johns Hopkins Hosp	149 (osteolytic)	Femur	60	4	0	0	1	2	1
Cade (1955) Westminster and Mount Vernon Hosp, London	133	About knee	69	4–5	0	0	0	4	1 in ? vert
Dahlin (1957) Mayo Clinic	469	About knee	233	23	10	2	3	5	3

Table 4—*Continued*

Author	No of Cases	Most Frequent Site	No	Chest No	Ribs	Sternum	Clavicle	Scapula	T Vert
Simple Bone Cyst									
Silver (1912) Literature	97	Femur	31	3	0	0	3	0	0
Coley (1949) Memorial Hospital	52	Humerus	26	2	2	0	0	0	0
Geschickter and Copeland (1949) Johns Hopkins Hosp	230	Femur	77	7	2	0	4	0	1
Giant Cell Tumor									
Geschickter and Copeland (1949) Johns Hopkins Hosp	199	About knee	103	7 to 8	2	0	1	4	1 in ? vert
Windeyer and Woodyatt (1949) Middlesex Hospital, London	38	About knee	9	1+	0	0	0	1	5 in ? vert
Prossor (1949) Westminster Hospital, London	25	Humerus	6	0	0	0	0	0	0
Murphy and Ackerman (1956) Barnes Hospital	26	About knee	12	2	0	0	0	0	2
Dahlin (1957) Mayo Clinic	109	About knee	64	1	1	0	0	0	0
Coley et al (1958) Memorial Hospital	108	About knee	52	4	2	2	0	0	0
Malignant Giant Cell Tumor									
MacGuire and McWhorter (1924) Presbyterian and Bellvue Hospital	20	About knee Femur	13 5	0	0	0	0	0	0
Simmons (1931) Bone Sarcoma Registry (1925)	116	Femur	36	5+	2	00	0	3	4 in ? vert
Geschickter and Copeland (1949) Johns Hopkins Hosp	7	Humerus	2	1–2	0	0	0	1	1 in ? vert
Murphy and Ackerman (1956) Barnes Hosp, St Louis	5	Femur	3	0	0	0	0	0	0
Dahlin (1957) Mayo Clinic	11	About knee Femur	9 7	0	0	0	0	0	0
Coley et al (1958) Memorial Hospital	15	About knee	7	0	0	0	0	0	0
Ewing's Tumor									
Morton (1940) Bone Sarcoma Registry	200	Tibia Femur	39 38	28	13	0	8	7	0
Geschickter and Copeland (1949) Johns Hopkins Hospital	167	Femur	40	20	7	0	5	8	0
Coley (1949) Memorial Hospital	149	Femur Pelvis	42 24	33	24	0	5	4	0
Wang and Schulz (1953) Massachusetts General Hospital	50	Femur	9	10	9	0	1	0	0
Dahlin (1957) Mayo Clinic	141	Femur	37	26	10	1	6	8	1

TABLE 4—*Continued*

Author	No of Cases	Most Frequent Site	No	Chest No	Ribs	Sternum	Clavicle	Scapula	T Vert.
Nonosteogenic Fibroma of Bone									
Jaffe and Lichtenstein (1942) Hospital for Joint Disease, New York	10	Tibia Fibula	4 4	0	0	0	0	0	0
Devlin et al (1955) *Henry Ford Hospital*	6	Tibia	4	0	0	0	0	0	0
Maudsley and Stansfeld (1956) Royal Free Hosp , London	10	Tibia	7	0	0	0	0	0	0
Dahlin (1957) Mayo Clinic	35	Tibia	14	2	2	0	0	0	0
Fibrosarcoma of Bone									
Geschickter and Copeland (1949) Johns Hopkins Hosp	31	Distal femur	9	3	1	0	0	2	0
Dahlin (1957) Mayo Clinic	58	Distal femur	14	5	1	0	0	4	0
Hemangioma of Bone									
Thomas (1942) Bone Sarcoma Registry	12	Skull Tibia Vertebra	2 2 2	2	0	0	0	1	1
Dahlin (1957) Mayo Clinic	13	Skull	9	2	0	0	0	0	2
Malignant Angioma									
Thomas (1942) Bone Sarcoma Registry	15	*Femur*	3	1	1	0	0	0	0
Coley (1949) *Memorial Hosp*	11	Scapula	3	5	2	0	0	3	0
Chordoma									
Mabrey (1935) Literature	150	Sacrum	87	2	0	0	0	0	2
Heaney et al (1956) Cleveland Clinic	19	*Cranial*	9	1	0	0	0	0	1
Dahlin (1957) *Mayo Clinic*	80	Sacrum	43	3	0	0	0	0	3

Pain associated with pronounced tenderness is the most common complaint. The pain is aggravated by activity and relieved by rest; in contrast to other malignant tumors, it is stated to be uncommon at night. A soft, non-pulsatile expansile swelling may be found in the involved bone. The radiologic features are of two types: (1) osteolytic, which is purely destructive

TABLE 5—*Conditions Simulating Chest Wall Neoplasms*

Conditions	Of Soft Tissues	Of Bone
Normal anatomic relationships—Misinterpreted Congenital abnormalities	—breast* —nipple* —polythelia —polymastia	—center of ossification* —prominent xiphoid —hypertrophied costal cartilage —pigeon breast —rib anomalies* —infantile cortical hyperostosis*
Post-traumatic Conditions	—foreign body —hematoma —myositis ossificans* —fat necrosis —post-traumatic cyst —muscle rupture —muscle hernia —lung hernia	—fracture (especially rib) —costochondral separation
[illegible] brucellosis, actinomycosis, blastomycosis, coccidiomycosis, histoplasmosis, sporotrichosis, anthrax, sarcoidosis)	[illegible] —empyema necessitans —plasma cell mastitis —nodular nonsuppurative panniculitis	—osteomyelitis* —osteochondritis* (Carre) —hydatid cyst* —infectious arthritis —hypertrophic arthritis —rheumatoid arthritis —gout
Circulatory disturbances	—edema and myxedema —aortic or intercostal artery aneurysm —thrombophlebitis of chest wall vein (Mandor's disease)	—aseptic necrosis* (Caisson disease) —aneurysmal bone cyst* —spontaneous absorption of bone* —rib notching from increased collateral circulation*
Nutritional and metabolic disturbances	—amyloidosis —calcinosis —xanthoma tuberosum	—rickets —scurvy —hypervitaminosis A —lipid reticuloendotheliosis* —sprue*
Endocrine disturbances	—gynecomastia	—hyperparathyroidism* —acromegaly
Collagen disorders	—dermatomyositis —periarteritis nodosa —circumscribed scleroderma (morphea)	
Conditions of unknown etiology	—chronic cystic mastitis —psoriasis —acanthosis nigricans	—fibrous dysplasia* —Paget's disease of bone* —melorheostosis* —osteopoikilosis* —Tietze's syndrome
Intrathoracic tumors	—mediastinal* —pericardial* —pulmonary* —diaphragmatic*	

* Conditions important from the standpoint of radiographic interpretation

and shows sharply defined punched out areas without trabeculations or (2) multicystic, which is also sharply demarcated but may expand the bone without producing cortical destruction or periosteal reaction. Fractures are frequently seen in this latter type, and these lesions are believed to be less likely to metastasize The serum protein level may be elevated, but Bence-Jones proteinuria is uncommon in myeloma of the thoracic wall[40] Diagnosis must be based on biopsy. Needle aspiration should be done if there is good evidence of multiple myeloma (multicentric lesions, characteristic plasma electrophoretic pattern) The tumor is radiosensitive but when it appears solitary and accessible it is probably best excised. If the disease is disseminated, urethane treatment is indicated with irradiation of the painful areas. Some cases have been cured but usually other foci of myeloma appear in time.

A primary malignant lymphoma of bone is most commonly composed of reticulum cells. Such a tumor should be differentiated from secondary involvement of bone in malignant lymphomas and leukemia, and from Ewing's sarcoma, since these tumors have a much poorer prognosis Usually, it is a solitary lesion occurring in young men. Pain is often of long duration with ultimate development of swelling. The tumor may become extremely large while the patient continues to maintain a sense of well-being. In general, a localized osteolytic "cracked ice" appearance is demonstrable roentgenographically Often cortical bone is destroyed and there is evidence of reactive new bone proliferation within the tumor The tumor is radiosensitive but excision is the best therapy. It may metastasize to the regional lymph nodes so this area should be treated as well. Without treatment, a localized lymphoma may eventuate into a systemic disease but with treatment it has the best prognosis of any malignant tumor of bone.

Cartilaginous Tumors

The most common benign tumor of the thoracic cage is osteochondroma, which is frequently multiple The chondromas are also frequently seen, but chondroblastomas are rare and chondromyxofibromas are rarer. Of the 36 reported cases of chondromyxofibroma, 5 were in the thoracic wall[18] Benign tumors occur most frequently in persons in the second decade of life; they usually complain only of a mass, which may have been present for many years. Ten per cent of patients with benign tumors will initially have only pain The tumors are usually small but chondromas may be extremely large. The roentgenographic picture of an osteochondroma is almost pathognomonic, showing the tumor on a broad stalk, the medulla and cortex being continuous with that of the underlying bone. Irregular calcific deposits may be seen in the cartilaginous cap. The other benign tumors show a central well defined area of rarefaction with stippled or mottled

calcification, the lesion often expanding the bone, but the cortex remaining intact Since almost all chondromas and a large number of other benign cartilaginous tumors will become malignant in time, wide local excision is recommended This is particularly important if the tumor is large, painful or growing, since it already may have undergone malignant transformation. These criteria are also useful in the management of multiple cartilaginous neoplasms seen after adolescence The histologic picture of benignancy is not in itself absolute evidence since numerous reports in the literature demonstrate that a "benign" tumor may recur after resection, and the same patient may even die years later from chondrosarcoma

Malignant cartilaginous tumors (chondrosarcoma) are even more common in the thoracic wall than benign ones Two forms are recognized: primary, and secondary, those developing from benign cartilaginous tumors Primary chondrosarcomas occur most frequently in the postadolescent male They are less common in the thoracic wall than the secondary forms The usual history is of short duration consisting of progressive pain and development of a tender, firm, nodular tumor, often after trauma Late systemic symptoms (fever and weight loss) are common, and regional lymphadenopathy may be present A semitranslucent density lifting the periosteum and destroying the underlying bone (in the case of a rib often the entire width) is demonstrable roentgenographically The tumor is highly malignant, making radical excision the only treatment Although it is radioresistant, roentgenography does relieve pain and should be employed if surgical treatment is contraindicated or refused

Secondary chondrosarcomas are seen in an older age group (35 to 55 years) Symptoms suggestive of a pre-existing benign tumor (smooth, nontender, hard mass) have usually been present for a long time (years) with recent increase in growth and progressive pain There may be roentgenographic evidence of the underlying benign process in addition to the sarcoma, which has a more granular stippled or flocculent appearance than seen in the primary forms. Secondary chondrosarcomas grow more slowly than the primary forms, perhaps influenced by the older age of these patients Again, radical excision is indicated, and the prognosis is somewhat better

Metastasis occurs often after several recurrences It is usually hematogenous but is also common in the epidural space, suggesting extension along the intercostal veins to the vertebral veins [32]

Osseous Tumors

Benign osteogenic neoplasms occur only rarely in the thoracic wall and are not considered premalignant lesions Osteomas and osteoid osteomas have been found almost entirely in the scapula, whereas osteoblastomas

have been reported only in the thoracic vertebrae. An osteoma is demonstrated roentgenographically as a dense, smoothly outlined shadow without showing destruction of bone or irregular calcific deposits, which are characteristic of osteochondroma Excision is indicated if the tumor grows large enough to produce pressure symptoms. The roentgenographic picture of an osteoid osteoma is almost pathognomonic, having an oval area of translucency surrounded by a ring of sclerotic bone. These lesions are extremely painful, often awakening the patient at night. Excision is recommended. *Osteoblastomas* also produce pain usually by pressure on the intercostal nerves The roentgenogram demonstrates more or less circumscribed bony destruction which may have sclerotic bone reaction at its edges. The tumor should be excised if possible but usually one must be satisfied with curettement.

Osteogenic sarcoma is the most common primary malignant tumor of bone However, in the thoracic wall it occurs infrequently compared with chondrosarcoma.[31] It may develop in any bone of the thoracic wall (table 4) It may even be found in the soft tissues.[3] The tumor may be encountered in patients of any age, but, whereas the osteogenic sarcomas in general have a peak incidence in the second decade, most of those reported in the chest have occurred in older adults. The scapula is a common site in patients older than 50 years of age.[5] Pain, the earliest symptom, is a constant finding and is rarely of more than one year's duration. An irregular, firm, nontender mass, usually in the posterior portion of the ribs, is almost always present. The skin may be shiny, smooth and stretched tightly over the lesion. The alkaline phosphatase level is usually elevated, decreases with effective treatment but rises again with recurrence of the tumor.[23] The roentgenographic picture is that of a destructive lesion with indistinct borders, frequently periosteal reaction when the cortex is intact, and variable amounts of new bone formation within the tumor, even to the degree of being heavily ossified and considerably eburnated The greater the amount of osteogenesis, the more likely the diagnosis. When there is considerable ossification beyond the cortex, the radiating striations present the "sun-burst" pattern. The relatively unossified lesion is probably necrotic, cystic and telangiectatic and the most likely to develop a pathologic fracture. These tumors metastasize early and should be considered highly malignant. Spread is almost exclusively hematogenous (to lungs), although rarely regional lymph node and skeletal metastases do occur. Radical surgical excision is desirable for cure, and although the tumor is considered to be radioresistant, in most of the cures of lesions of the thoracic wall, postoperative irradiation has been employed. If excision is not possible, irradiation should be tried because Coley[5] reported a cure with this treatment

alone It is also considered worthwhile to resect solitary pulmonary metastatic lesions from osteogenic sarcoma

Parosteal osteogenic sarcomas have not been reported in the thoracic wall

Tumors of Undetermined Origin

Simple bone cysts may occur in ribs or clavical but are rare in any other bones of the thoracic wall However, they are common tumors demonstrated rather frequently in roentgenograms of the chest since a common site of this neoplasm is the head of the humerus. They are most frequent in children and adolescents, particularly males There are usually no symptoms before development of a fracture The roentgenographic feature is a circumscribed radiolucency producing a fusiform widening of the bone The cortex is thinned but remains intact unless there is a fracture Irradiation must be avoided since malignant changes have developed only after such therapy[5] Resection is indicated to confirm the diagnosis

Giant cell tumors, benign and malignant, are rare in the thoracic wall They are seen in young adults, predominantly women 20 to 40 years old, a group older than the patients with simple bone cysts Whereas simple cysts are most likely to be found in the anterior portions of the ribs, giant cell tumors are located in the epiphyses of the bone (the head and tubercle of the ribs). The roentgenographic appearance is that of a well circumscribed cystic expanding lesion with thin trabeculae traversing the cystic space. Ten per cent of benign tumors undergo malignant transformation so that resection is desirable In inaccessible regions (vertebra), treatment with moderate doses of roentgenray may promote healing[27] The malignant giant cell tumor may have a more destructive appearance roentgenographically but a preoperative diagnosis is unusual unless the lesion represents the recurrence of a treated benign giant cell tumor

Ewing's tumor is a common malignant bone tumor which occurs relatively often in the thoracic wall (table 4) of young children and adolescents. Many believe that it represents metastatic neuroblastoma rather than a separate entity The clinical picture is characterized by pain, fever and swelling with alternating periods of remissions and exacerbations Often, the tumor is confused with an inflammatory process The roentgenographic picture is usually one of bone destruction, sometimes with an associated extraosseous mass The pathognomonic laminated appearance ("onion peel") has been overemphasized At times there is the "sun-burst" appearance that is typical for osteogenic sarcoma Ewing's tumor is the most malignant of all bone tumors and spreads early to other bones, but not readily to soft tissue It is radiosensitive and should be treated with roentgen-ray even when excision has been done for biopsy

Fibrous Tumors

The benign fibrous tumor of bone (nonosteogenic fibroma) may be a variant of fibrous dysplasia. Although a common benign bone tumor, it is rarely found in the thoracic wall (table 4). It generally produces no symptoms, being discovered solely on roentgenographic examination. The roentgenographic picture is believed to be diagnostic—a rarefied, loculated appearing area which thins out and tends to bulge the cortex while its inner boundary is demonstrated by a thin or scalloped line of sclerosis Observation is justified if one feels confident of the roentgenographic diagnosis, but conservative excision or curettage is safer.

Fibrosarcoma of bone is a connective tissue sarcoma which begins within a bone and in the chest is most frequently found in the scapula (table 4). Patients usually complain of pain and swelling of short (months) duration. The roentgenographic picture cannot be differentiated from the osteolytic type of osteogenic sarcoma This tumor is extremely radioresistant Treatment is the same as for osteogenic sarcoma.

Vascular Tumors

Hemangioma of bone is rarely found in the thoracic cage aside from the vertebrae. Such a tumor produces only pressure symptoms, persistent backache being the most common. The roentgenographic appearance in the vertebra is that of vertical striations, but in the ribs and clavicle there is a "soap bubble" appearance, and in the scapula and sternum there is a "sunburst" appearance with trabeculations radiating from a common center. The tumor is best excised but in the vertebra repeated moderate doses of roentgenray restrain growth with resultant recalcification of damaged bone.[30]

Malignant angiomas of bone are uncommon. They usually involve the scapula (table 4) and rarely, if ever, the vertebrae, as benign hemangiomas do *Angiomas produce pain and swelling with occasional increased temperature* and cardiac murmur.[5] Treatment is wide excision.

Adipose Tumors

Lipogenic neoplasms arising within the bone *are extremly rare,* but both benign[6] and malignant tumors of this nature have been reported in the thoracic cage.

Neurogenic Tumors

The neurilemmoma of bone is usually a manifestation of Von Recklinghausen's disease It can be destructive, leading to severe deformity of the chest.

Notochordol Tumors

The chordoma is a rare tumor of low grade malignancy which will involve only the vertebrae primarily (table 4), and of these, the dorsal vertebrae least frequently. Pain of long duration is the prominent symptom Destruction of bone is demonstrable roentgenographically. Excision is the ideal treatment but irradiation should be employed if this is not feasible

Tumor of Undifferentiated Mesenchyme

Myxomas of bone have been reported in the thoracic wall in the periosteum of the clavicle[44] and the rib, but according to Jaffe[21] and Lichtenstein[25] this neoplasm never occurs outside the jaw It is treated by wide local excision because of its tendency to recur

SECONDARY NEOPLASMS

Secondary neoplasms are more common than primary tumors in the thoracic wall They result from (1) direct invasion by tumors of the contiguous organs or (2) metastases from distal neoplasms

The most frequently occurring secondary neoplasm in the thoracic wall of a child is a neuroblastoma, in women, carcinoma of the breast, in men older than 40 years, carcinoma of the prostate and in those younger than 40 years, renal cancer Invasion by bronchogenic carcinoma is also relatively common The secondary neoplasm may be the first manifestation of malignant disease The presenting symptom is usually dull, aching pain, most often due to involvement of an intercostal nerve Swelling and tenderness may be present as well Occasionally, the first sign is an asymptomatic tumor, with roentgenographic evidence of a bone lesion or a pathologic fracture Metastasis to the thoracic wall may be hematogenous or lymphogenous Nonosseous metastasis is commonly to the skin but occasionally to the subcutaneous tissue and only rarely to the muscles. The tumors most frequently metastasizing to the soft tissues of the thoracic wall arise in the breast, stomach, uterus or kidney The leukemias and malignant lymphomas may also infiltrate these tissues and the bone marrow. Osseous metastasis is otherwise most common from neoplasms of the breast, prostate, lungs, thyroid, kidney and rectum The ribs and vertebrae are the bones of the thoracic wall most commonly involved with metastatic disease. The lesions are usually destructive (osteolytic) but they may be osteoblastic

Management of secondary neoplasms will depend on (1) the index of suspicion as to its secondary nature (2) control of the primary tumor (3) location and size (particularly multiplicity) of the secondary lesion and (4) the discomfort it produces Histologic proof of its nature is desirable but occasionally the roentgenographic features are so typical that this is

not necessary for treatment. If metastatic disease is strongly suspected, aspiration biopsy should be done. If the lesion appears to be single and is well localized in an accessible area, it should be excised. Further treatment (radiotherapy, chemotherapy, radical surgical procedures, etc.) will have to be decided on for each case on an individual basis.

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CHAPTER 16

Tumors of the Diaphragm

By ALTON OCHSNER, SR., M.D., AND ALTON OCHSNER, JR., M.D.

Incidence

PRIMARY NEOPLASMS OF THE DIAPHRAGM are uncommon. Records of 67 cases have been found in the literature[2, 12] since the first report by Grancher[5] in 1868 In addition, one case of primary neoplasm in the diaphragm of a cow[12] and 2 clinical cases without histologic confirmation[12] have been reported.

Histologic Type

All tumors of the diaphragm should be of mesenchymatous origin but a few representing aberrant tissues, such as liver and adrenal, have been reported Almost as many of the reported tumors have been malignant as benign; there were 34 benign and 33 malignant tumors.

Benign tumors usually arise from the tendinous portion of the diaphragm, often on a pedicle. The commonest reported benign tumor was lipoma, but a benign neoplasm of the diaphragm is more likely to have fibrous tissue elements than fat or even muscle Among the benign tumors were 7 lipomas, 3 each angiofibromas, neurofibromas and fibromyomas, 2 each hepatic adenomas, lymphoangiomas and neurilemmomas, and one each adrenal cortical adenoma, chondroma, dermoid cyst, fibrolipomyxoma, fibrolymphangioma, fibroma, telangiectatic fibroma, hemangioma, leiomyofibroma, myoma, rhabdomyofibroma and teratoid cyst.

At times, it is difficult to differentiate even histologically the benign from the malignant lesions The most frequently reported primary malignant neoplasm was the fibrosarcoma, among the 33 cases there were 10 of these. The other 23 were 4 mixed cell sarcomas, 2 each neurofibromas, rhabdomyosarcomas and sarcomas, and one each angio-endothelioma, carcinoma, fibroangio-endothelioma, fibrosarcoma, hemangioendothelioma, leiomyosarcoma, mesothelioma, myosarcoma, undifferentiated myosarcoma, endothelial sarcoma, round cell sarcoma, spindle cell sarcoma and undifferentiated sarcoma

Many of the reported cases are obviously of the same histologic type but the descriptions are not adequate enough to permit accurate reclassification. Several were merely mentioned, no detailed clinical or pathologic description having been given.

Secondary neoplasms of the diaphragm are undoubtedly more common than primary ones, the stomach being the usual primary site The diaphragm is not, however, a frequent site of metastatic disease

Symptomatology

Diaphragmatic neoplasms may be encountered in patients of any age. The youngest reported case was in an infant 11 days old, who had a hemangio-endothelioma that had been symptomatic since birth [11] A mesothelioma of the diaphragm discovered at necropsy on an 80 year old woman has been reported [9]

Diaphragmatic neoplasms usually produce symptoms but occasionally are found on routine roentgenography of the chest or incidentally at necropsy Lipomas generally are asymptomatic The most frequent symptom is pain in the lower part of the chest or at times in the flank on the side of the lesion Usually, the pain is accentuated with deep inspiration If the phrenic nerve is involved, the pain may be referred to the shoulder and neck In at least 4 of the reported cases, the patients had articular pain (pulmonary osteoarthropathy), *which was relieved by excision of the tumor* *Sensation* of fullness in the chest and dyspnea on exertion are also common complaints Infrequently, cough, hemoptysis, nausea, anorexia and loss of weight are present

The physical signs appear to be related to the size of the tumor Usually, dullness due to the neoplasm or associated pleural effusion is demonstrable at the base of the thorax Decreased breath sounds, increased tactile fremitus and limitation of excursion of the base of the lung are detected on physical examination In 8 of the reported cases, examination revealed a [illegible] or itself or displaced [illegible] iastinum and heart [illegible] producing impaired cardiac filling and edema of the lower extremities A tumor covered by large blood vessels which produced a murmur has been described in the literature [7] Clubbing of the fingers may also be present

Roentgenography

The diaphragm is a thin flat muscle which usually has a smooth superior surface easily outlined by the aerated lung It is unlikely, therefore, that a tumor of any size can develop without some roentgenographic evidence of its presence on even postero-anterior and lateral roentgenograms of the chest. However, most radiographic deformities of the diaphragm are not produced by neoplasms! The roentgenographic appearance of a neoplasm is determined by the size and shape of the tumor and the amount of pleural reaction induced by it The least suspicious picture is produced by a dif-

fusely enlarged diaphragm which gives the initial impression of "elevation" Such *enlargement from* a neoplasm, however, should cause some displacement of the lower mediastinal structures into the opposite hemithorax and of the abdominal organs downward. It may also be associated with widening of the lower intercostal spaces and destruction of the lower ribs.[8] Pleural fluid may conceal a diaphragmatic tumor until the fluid is removed or shifted away from the diaphragm by *proper positioning of the* patient. Usually, however, the picture is that of a localized, convex shadow confluent with the diaphragm with a sharply defined but occasionally lobulated surface. The protrusion is usually into the thoracic cavity and is *sometimes* superimposed on the cardiac shadow[2] but may appear in the gastric bubble.[6] A localized deformity is more likely to represent a benign process, whereas an extensive shadow that obliterates the lower portion of the thoracic cavity is more suggestive of a malignant neoplasm. However, no roentgenographic picture is pathognomonic of a diaphragmatic neoplasm

Diagnosis

The roentgenographic picture described in the preceding paragraph can *be produced by lesions both above and below the diaphragm as well as by* non-neoplastic diaphragmatic conditions (table 1). Nonspecific diaphragmatic cysts deserve special consideration since they are frequently considered with primary neoplasms Eighteen such cysts[12] have been reported, 10 of which were mesothelial, 5 bronchogenic and 3 fibrous walled Three or 4 of the mesothelial tumors may actually have been pleural cysts of the dia-

TABLE 1—*Conditions Simulating Primary Neoplasm of Diaphragm*

Supradiaphragmatic	Intradiaphragmatic	Infradiaphragmatic
OF PLEURA Cyst, neoplasm, encapsulated pleural effusion, fibrin body, loculated empyema, pericardial fat *pad* OF LUNG Sequestrated lobe, cyst, abscess, neoplasm OF PERICARDIUM Cyst, neoplasm *OF ESOPHAGUS Enteric cyst,* reduplication, neoplasm OF THORACIC WALL Neoplasm, infection	NORMAL VARIATIONS Polyarcuate appearance, anteromedial bulge PHRENIC NERVE PARALYSIS *Complete, segmental* CYSTS Developmental, tuberculous, echinococcus INFECTIONS Acute primary diaphragmitis (Joannides-*Hedblom syndrome)* abscess, granuloma (tuberculous, syphilitic, nonspecific) VASCULAR Hematoma, myositis ossificans, aneurysm of phrenic vessels, metastatic neoplasm	OF PERITONEUM Eventration of diaphragm, diaphragmatic hernia, subdiaphragmatic abscess, subhepatic abscess OF LIVER Hepatomegaly, neoplasm, abscess (pyogenic or amebic), cyst (echinococcus), anomalous lobe, *hypertrophied* lobule OF SPLEEN Splenomegaly, neoplasm, abscess OF STOMACH Neoplasm OF KIDNEY ADRENAL Neoplasm

phragm Of the 18, only 3 were asymptomatic, the usual complaint was thoracic pain and dyspnea. All cysts were in adults but some had been present for many years.

Many of the conditions that simulate primary neoplasms of the diaphragm can be differentiated from them only by histologic examination. However, a thorough diagnostic study should be done before surgical exploration, because some lesions, such as diaphragmatic hernias, can be diagnosed without operation, and it is important to know preoperatively whether a lesion is supradiaphragmatic or infradiaphragmatic, since the surgical approach of each is different

There are a number of investigative procedures that may prove of value. These include routine roentgenography of the chest after aspiration of pleural fluid, fluoroscopy, pneumoperitoneum, pneumothorax, esophagography, roentgenography of the upper gastrointestinal tract, pyelography, skin and serologic tests, examination of pleural fluid, bronchoscopy, thoracoscopy, needle biopsy and thoracotomy

Normal roentgenographic variations in the contour of the diaphragm must be recognized Previous roentgenograms may demonstrate that the abnormal shadow has existed for a long time without increase in size, this would suggest a non-neoplastic lesion Calcification is suggestive of a chronic inflammatory lesion, such as a tuberculous or echinococcal cyst, and is always present in myositis ossificans Questionable calcification has been described in the roentgenogram of only one reported diaphragmatic neoplasm[4] in which osteoid tissue was found on histologic examination By fluoroscopy it is easier to determine the organ causing the roentgenographic shadow A diaphragmatic tumor usually causes little disturbance in diaphragmatic function and moves synchronously with the diaphragm and not independently, as a subdiaphragmatic lesion is likely to do Diaphragmatic paralysis should be recognized An extensive invasive neoplasm may fix a diaphragm as does inflammation

In the absence of adhesions, air injected into the pleural and peritoneal cavities, should separate the intrathoracic and intra-abdominal organs from

visualization of the gastrointestinal tract with contrast media is useful in demonstrating a diaphragmatic hernia or an intrinsic gastric lesion, but a primary neoplasm of the diaphragm can produce a filling defect of the stomach so that the need for pneumoperitoneum is not always obviated Pyelography is helpful if a kidney or adrenal tumor is suspected. Skin and serologic tests are useful in the differential diagnosis of tuberculous, syphilitic and echinococcal lesions Examination of the pleural fluid for malig-

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CHAPTER 17

Tumors of the Esophagus

By FRANCIS M WOODS, M.D

TUMORS OF THE ESOPHAGUS PRESENT a therapeutic challenge infrequently overcome Sufficiently early diagnosis is rarely possible because the major complaint, difficulty in swallowing, ordinarily does not occur until the tumor has invaded the entire circumference of the esophageal wall In addition, tumors of the upper two-thirds arise within millimeters of the trachea, aorta and pericardium, thus often invading vital structures even before symptoms have developed

SYMPTOMS

The major symptoms are dysphagia and regurgitation Dysphagia first noted with solid foods, progresses gradually to make it impossible to swallow soft and finally even liquid foods The level at which the obstruction occurs is sensed accurately Mild pain on swallowing is not necessarily indicative of extension beyond the esophagus, but, constant pain, which may be felt anywhere along the course of the esophagus or even in the upper abdomen, is usually a sign of invasion of the surrounding tissues On occasion, a tumor not obstructing the lumen but only invading periesophageal tissues causes pain without dysphagia Since the usual diagnostic procedures depend on recognizing a level of obstruction in the esophagus, the true explanation is easily overlooked for long periods of time. Regurgitation of saliva and undigested food into the pharynx is the result of overflow of material dammed above an obstructing tumor Aspiration of such material leads to cough and at times tracheobronchial infections Inadequate ingestion of food, leads to weight loss, weakness, hypoproteinemia and anemia Cough suggests invasion of the trachea, hoarseness suggests involvement of the recurrent laryngeal nerves Signs of caval obstruction suggest massive mediastinal invasion

PATHOLOGY

The majority of tumors of the esophagus are malignant, and of these nearly all are epidermoid carcinoma In the series at the Overholt Thoracic Clinic we have encountered 83 epidermoid carcinomas of the esophagus and only 2 benign tumors Adenocarcinomas found in the lower end of the esophagus undoubtedly actually arise in the stomach, but may produce esophageal obstruction The rare benign tumors usually occur in the esophageal

wall and are usually leiomyomas, but fibromas, polyps and cysts are reported Polyps have been known to develop long pedicles and have been regurgitated into the pharynx. Symptoms, if any, in the case of benign tumors are also those of obstruction, but according to Boyd and Hill only 7 of 17 gave a history of obstruction; the others were incidental findings

Diagnostic Procedures

Because of the inaccessibility of the organ, physical examination is not revealing except for evidences of wasting Barium swallow reveals a shelf-like deformity characteristic of esophageal carcinoma (fig 1) and may occur at any level. Benign tumors show a smooth rounded indentation from one side of the esophagus suggesting extrinsic pressure (fig 2). Differential diagnosis is usually easy but diverticuli, external compression from mediastinal tumors and stenosis from esophagitis or corrosive agents have to be

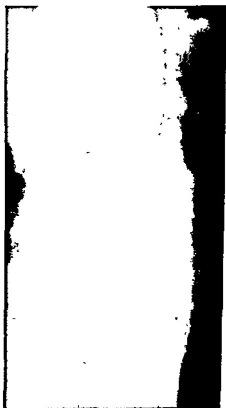




Fig 1—(*left*) Barium swallow illustrating typical roentgenogram appearance of carcinoma of the esophagus Note the shelf-like deformity and threadlike opening in the remaining esophagus

Fig 2—(*right*) Barium swallow illustrating typical appearance of benign tumor of the esophageal wall Note the lateral indentation

considered Esophagoscopy will establish the diagnosis in most instances of carcinoma, for a fungating tumor can be seen and a biopsy can be taken Bronchoscopy is indicated in all tumors of the upper two-thirds because of the possibility of direct invasion of the trachea or main bronchi Care must be taken not to overlook the correct diagnosis when a positive biopsy is not obtained Not infrequently, the tumor burrows submucosally and pushes normal mucosa up ahead of it so that the biopsy shows only mucosa In the case of benign tumor the esophagoscopic appearance is that of external compression. Through the esophagoscope it is easy to overlook malignant tumors involving only part of the circumference of the esophageal wall or benign tumors in the wall, for the esophagoscope may slide by such an area The endoscopist must make a practice of inspecting the complete circumference of the esophageal wall at all levels

Treatment

Treatment of benign tumors is relatively easy and highly satisfactory. Treatment of malignant tumors is difficult and at the present time unsatisfactory The benign tumors, which nearly all involve the esophageal wall and do not protrude through the mucosa, can be excised locally, usually without opening the mucosa The surgical approach is transthoracic from either the right or left side The esophagus is approached and isolated in the area where the tumor exists The muscular layers of the wall are split longitudinally over the tumor, the tumor is shelled out, and the muscle layers reapproximated. Polyps may be removed endoscopically or by direct approach through the esophageal wall.

Treatment of malignant tumors of the esophagus varies according to the level at which the tumor occurs The percentage of long-term survival is small at any level but improves the lower one goes in the esophagus A long-term survival is a rarity in the cervical portion and the upper two-thirds of the esophagus There are appreciable numbers in the lower part of the esophagus Most attempts at treatment should be considered palliative procedures for the possibility of complete excision is not the rule. The early attempts to palliate consisted in gastrostomy purely for feeding purposes This rarely proved to be a kindness to the patient because even though not attempting to swallow food constant regurgitation of esophageal secretions back into the pharynx continued the patient on a miserable downhill course Torek is credited with the first successful resection of the esophagus He resected the esophagus transthoracically and brought out the stump of the cervical esophagus into a subcutaneous position Later an antethoracic esophagus, fashioned from skin tubes, created a direct communication from the cervical esophagus to a gastrostomy. The technical difficulties in multiple operations necessary to do this have led to abandonment of the principle

Variations of the plan first developed by Adams and Phemister are the most used procedures. They opened the chest and abdomen through a thoraco-abdominal incision on the left, resected the esophagus, and brought up the fundus of the stomach into the left chest and made a primary anastomosis between the stump of the esophagus and the stomach. It is entirely possible to resect the entire length of the esophagus in this manner and to bring the fundus of the stomach up to the apex of the chest or even into the neck if necessary. This left-sided approach is a satisfactory procedure for carcinomas of the lower third of the esophagus. However, when one gets up into the upper and middle thirds of the esophagus and has to work behind the arch of the aorta it requires mobilization of part of the aorta and division of intercostal arteries which creates technical difficulties. It is, therefore, our preference to resect the esophagus from the right side of the thorax where simple division of the azygous vein gives ready access to the entire thoracic esophagus (fig 3). We have twice succeeded in resecting the esophagus from the right side when it had previously been approached from the left side and con-

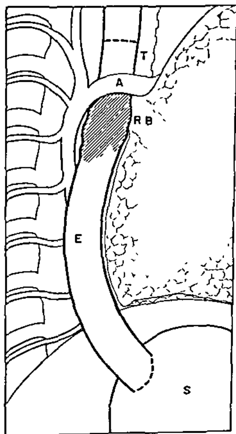


Fig. 3—Exposure of the entire thoracic esophagus through a right thoracotomy incision Note that after the azygous vein is divided the entire organ is easily accessible The tumor is represented by shaded area

A—Azygous Vein
T—Trachea
RB—Right Bronchus
E—Esophagus
S—Stomach

sidered unresectable. The right-sided approach requires a separate abdominal incision for mobilization of the stomach. Combined thoraco-abdominal incisions on the right are not satisfactory.

Our present plan of surgical treatment is as follows For carcinoma of the lower third of the esophagus either the right or left approach may be used. If the left side is elected, the plan is that described by Adams and Phemister. If the right side is chosen the plan is that described below. For all carcinomas in the upper two-thirds of the esophagus or the cervical esophagus the right-sided approach is used The patient must be carefully prepared by adequate hydration and transfusions Even in the presence of a normal red blood count and hematocrit, transfusions are given preoperatively if there has been appreciable weight loss Blood volume determinations may be helpful in assessing the need of preoperative transfusions The first part of the operative procedure consists of a long vertical abdominal incision extending up to the xiphoid process The stomach is freed so that it can be [illegible]

serve the right gastroepiploic and gastric vessels The left gastric artery coming from the celiac axis and the left gastroepiploic artery coming from the splenic artery are divided At times, the spleen is taken. Often, invasion of the retroperitoneal glands is found Wherever possible, such glands are removed with the specimen If these glands cannot be successfully removed, the procedure should be completed for palliative purposes This would be true even if metastases in the liver were found When the stomach is completely free a pyloroplasty is performed by splitting the pyloric muscle longitudinally down to the mucosa This is done in order to avoid postoperative obstruction due to pylorospasm which is likely to occur because of the subsequent injury or resection of the vagus nerves If this is not done a breakdown of the esophagogastric anastomosis due to gastric retention is more frequent In addition gastric ulcer is reported by Smith, Mouldin [illegible] Adams as a late sequela of esophagogastric anastomosis for carcinoma of the esophagus when pyloroplasty is not done We have even seen [illegible] ulcer penetrate into the thoracic aorta under these circumstances [illegible] massive gastrointestinal bleeding The immediate hemorrhage was [illegible] fully managed and the hole in the aorta sutured, but the patient [illegible] quently developed a false aneurysm at the site of repair, and fatal [illegible] rhage resulted one year later After the pyloromyotomy the [illegible] wound is closed using through and through stay sutures since [illegible] patients are in a state of poor nutrition

The patient is now turned on his side and the right thorax [illegible]

through a standard periscapular incision dividing from 2 to 4 ribs posteri in order to get adequate exposure of the esophagus. The mediastinal ple is opened and the esophagus identified When the azygous vein is divic the entire esophagus is exposed for ready dissection (fig. 3). The grea difficulty is encountered separating the esophagus from the trachea a bronchi. The blood supply in the lower two-thirds is from paired branc from the adjacent aorta which must be identified and ligated. In rec years it has been the rare instance in which we have not been able to res the esophagus, even though in most instances it has been impossible to g an adequate margin of normal tissue around the tumor. An attempt is ma to get at least 2 inches above palpable tumor. The thoracic part of the d section is the vital part of the operation. If the upper and middle thirds the esophagus are involved, this dissection is so much easier from the rig side, we feel that the advantages outweigh the disadvantage of having make a separate abdominal incision to free the stomach. Once the esophag is freed up, it is possible to pull the stomach up through the hiatus witho enlarging it Now, the esophagus is divided at its junction with the stomac In instances where the stomach is involved by the tumor, a portion of th stomach may be excised. The opening into the stomach is closed with double row of continuous chromic catgut suture reinforced with interrupte silk sutures. A round 2½ cm. opening is made on the anterior surface of th fundus of the stomach at the point farthest from the pylorus, which can no be drawn to the apex of the chest or even into the neck if necessary. In th latter instance, the pylorus will be brought to the level of the diaphrag without difficulty provided the stomach has been properly mobilized Anas tomosis is made between the round opening in the stomach and the esopha gus which is divided well above the tumor (fig. 4). The anastomosis con sists of a mucosal layer of interrupted silk sutures tied with knots on th inside, and an outer layer of mattress sutures which takes the full thicknes of the muscle on both sides The anastomosis is reinforced with omental o pleural flaps and tension is taken off the anastomosis by a series of suture to chest wall, holding the stomach well up into the chest A Levine tube is left in place in the stomach A Levine tube lying against an anastomosis is not a significant hazard Leaks at the line of anastomosis have fortunately been rare in our experience In those instances where the tumor is so high that the anastomosis cannot be made inside the chest, a third incision is made in the neck We prefer to make the incision transversely in the lines of the neck rather than along the border of the sternomastoid muscle as is conventional. In either case, the thyroid is rotated medially and the esopha-gus is identified behind the cervical portion of the trachea When it is neces-sary to mobilize this portion of the esophagus, it is done with the right thorax still open. The esophagus is pulled out through the neck incision

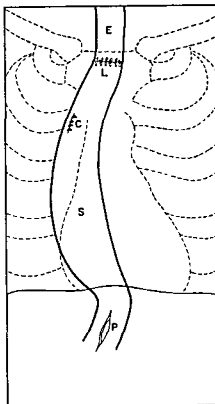


Fig 4—Diagram drawing showing completed esophagogastrostomy after resection of the entire thoracic esophagus through the right thorax Note the line of anastomosis (L) at the level of the thoracic inlet and the pyloromyotomy (P) at the level of the diaphragm
E—Esophagus
C—Closure of the stomach at the esophagogastric junction
S—Stomach

and the fundus of the stomach is drawn into the neck The anastomosis is made at that level, care being taken not to injure the recurrent laryngeal nerve

Such operations usually take a minimum of 4 and a maximum of 8 hours and require from 4 to 10 units of blood for support However, they are physiologically well tolerated Antibiotic therapy is an important adjunct to treatment, because it is impossible to make open anastomoses without contamination and secondary empyemas have been an occasional, but not a serious problem

Since we have been doing the described procedure, palliation has been far better It is true unfortunately, that the majority of these patients eventually show recurrences Recurrent tumor at the line of anastomosis is less frequent with the right-sided approach because more adequate resection has been possible Signs of tracheal or mediastinal invasion can be often alleviated by deep x-ray treatment

Deep x-ray therapy particularly with the 2 million volt units now avail-

able afford significant palliation in some patients as primary treatment. There are those who feel that the chances of significant palliation are better this way than with any form of surgery in the upper and middle thirds; however, we do not share this view. We have found high voltage x-ray therapy significant help when recurrence does appear particularly if the trachea is involved and cough and stridor develop. Attempts to palliate carcinoma of the esophagus with plastic tubes have been far from satisfactory. Carter advises inserting polyethylene tubes through the tumor endoscopically when resection is considered not feasible. Bringing up loops of small bowel instead of stomach to establish the continuity of the gastrointestinal tract is fraught with hazards because it is difficult not to impair the circulation of the small bowel which is brought high into the chest. There are reports of bringing up segments of right colon to replace or bypass the esophagus, but we have not had experience with this procedure and have not attempted it, because we have recently found that we can uniformly bring the stomach up and make a satisfactory anastomosis, thus, restoring the normal continuity of the gastrointestinal tract

SUMMARY

Benign tumors of the esophagus are rare but readily excised. Malignant tumors are common and amenable to only occasional cure by any form of therapy. Excision and primary restoration of gastrointestinal continuity by esophagogastrostomy in our hands offers the best possibility of cure and palliation Unless this continuity is restored there is no palliation.

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CHAPTER 18

Tumors of the Heart and Pericardium

By ISRAEL STEINBERG, M.D., AND HENRY P. GOLDBERG, M.D.

ALTHOUGH PRIMARY TUMORS OF THE HEART AND PERICARDIUM are rare, their diagnosis is important because the majority are benign and curable thanks to the new technics of open heart surgery.

Cardiac tumors are classified as metastatic and primary. The metastatic lesions may become manifest by the occurrence of irregularities of rhythm. The differential diagnosis depends on the finding of a primary cause for the malignancy and widespread metastases. Primary cardiac tumors may also be classified histologically or by location whether they predominantly involve the cardiac cavities (intracavitary), wall (intramural) or pericardium (intrapericardial). The clinical manifestations not only depend on the location of the tumor but whether they are benign or malignant.

Primary cardiac tumors were estimated to occur 0.05 per cent of all autopsies by Lymburner (1934) at the Mayo Clinic and 0.0017 per cent in a study of 480,331 cases by Strauss and Merliss (1945). Prichard reviewing the subject extensively in 1951 clearly established that myxomas are the most frequent primary cardiac tumors and are truly benign tumors of embryonic mesenchymal origin. Myxomas of the heart constitute about 50 per cent of the primary tumors of the heart. With few exceptions they have occurred in the atria; 75 per cent in the left and 25 per cent in the right. In almost every instance the tumor is polypoid and attached by a stalk to the foramen ovale or its rim (Mahaim). Microscopically, myxomas are contained within unbroken endocardium and have few cells. These are usually giant or multinuclear without mitoses and contain loose vascular tissue, hemorrhage, lymphocytes, plasmocytes, mucin-staining material and collagen.

Cardiac sarcomas are next in the order of occurrence of the primary tumors of the heart. Whorton (1949) reviewed the subject and found 99 cases in the literature and added a new one. Prichard, two years later, found a total of 113 cases and emphasized that the tumor tended to occur in the right atrium. In addition, hemopericardium and bizarre arrhythmias occur. The tumors may also begin in the right ventricle and are usually infiltrative or sessile, but 20 per cent (Mahaim, 1947) have polypoid structures projecting into the chambers. However, distant metastases occur in over 30 per

cent Histologically, the tumors have been "spindle cell" sarcomas (fibrosarcoma, fibromyxosarcoma, myosarcoma and leomyosarcoma; Prichard). Next in frequency are "round cell" neoplasms (lymphosarcoma, reticulum cell sarcoma or lymphoma). Rhabdomyosarcoma and angiosarcoma are other mesenchymal neoplasms belonging to this group (Prichard).

Only 12 benign angiomas of the heart, 5 hemangiomas and 7 lymphangiomas were reported by Prichard. In 4 of these, complete heart block was observed. The lesion was the cause of death in 5 patients and was an incidental finding in the remaining 7 cases. Fibroma of the heart is another rare cardiac tumor and is usually a single large tumor within the myocardium, most often the left ventricle or ventricular septum (Bigelow et al.; James and Stanfield). Calcification within a ventricular mass, arhythmias and heart failure with bizarre electrocardiographic changes have been suggested as criteria for diagnosis. Lipomas of the heart also have been only very rarely reported (Prichard) These occur subendocardially, subepicardially and intramurally.

Intracavitary Tumors

Intracavitary tumors originate almost exclusively in the atria The most characteristic clinical picture is that of stenosis, regurgitation or both at the mitral or tricuspid valves with no history of antecedent rheumatic fever. The growing tumor interferes with valvular function or mechanically obstructs the orifice of the valves Exertional dyspnea is common and when cardiac failure develops, it is usually intractable because of the mechanical interference with atrial or ventricular filling Cardiac output is severely reduced and may result in the development of angina. The systolic blood pressure is often low Fragmentation of tumor or dislodgement of surface thrombi may lead to clinical signs of embolization In some patients there may be definite knowlege of the absence of murmurs until the onset of the illness Other features include arhythmias, syncope, unexplained episodes of dyspnea, cyanosis, orthopnea, and variation in symptoms and auscultatory signs with change of position of the patient.

Conventional roentgenography in left atrial myxoma has regularly disclosed enlargement of the left atrium and pulmonary artery segment (Steinberg et al. 1953) These findings are indistinguishable from mitral stenosis due to rheumatic heart disease. When the myxoma occurs in the right atrium, enlargement of the chamber and widening of the superior vena cava may be expected. In three instances, a calcified right atrial mass was present and was clearly outlined by "fantastic" movements observed during fluoroscopy and cinefluorography (Buenger et al. [1956], Hopkins [1958], and Bahnson and Newman [1953]).

Cardiac catheterization data are available in several patients in whom

the diagnosis of myxoma has been proved—two with right atrial myxomas and the others with left atrial myxoma. In all cases there was evidence of obstruction to outflow from the atria. This consisted of abnormal elevation of atrial pressure. In the left atrial tumors, the pulmonary capillary pressures were also elevated. Cardiac output was reduced in the patients with the right atrial tumors; normal, in one patient with a left atrial tumor, and reduced, before or after exercise, in the others. It is doubtful that the catheterization data can be interpreted as revealing more than interference with atrial emptying. However, in the patient reported by Bayer and co-workers the catheterization data suggested the presence of a mass at the tricuspid valve. This is not a proven case although the angiocardiogram which was taken suggested a right atrial tumor. A fatality following cardiac catheterization in a patient with a myxoma was recently described by Svedberg and Stone.



Fig. 1—Right atrial myxoma in a 35 year old woman with tricuspid stenosis and recurrent chronic right heart failure. (A) Conventional frontal roentgenogram showing enlargement of the heart, especially the right atrium.

Angiocardiography has proved to be the definitive method of diagnosis of intracavitary tumor. Characteristic, persistent filling defects in an enlarged atrium were noted in all cases (figs. 1–4). Prolapse of the tumor (fig. 1B–E) during atrial systole may sometimes be recognized. The polypoid character of the tumor may also be recognized (fig. 1D and E). In the 3

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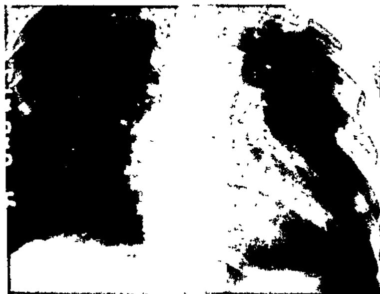


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Fig 1—(B) Angiocardiogram during atrial diastole shows a filling defect (tumor) in the right atrium

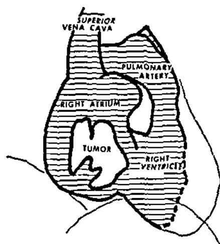


Fig 1—(C) Tracing of B



Fig 1—(D) Angiocardiogram during atrial systole shows the tumor prolapsed through the tricuspid valve into the right ventricle

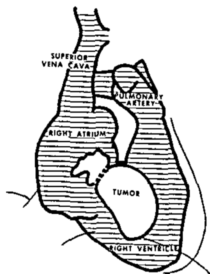


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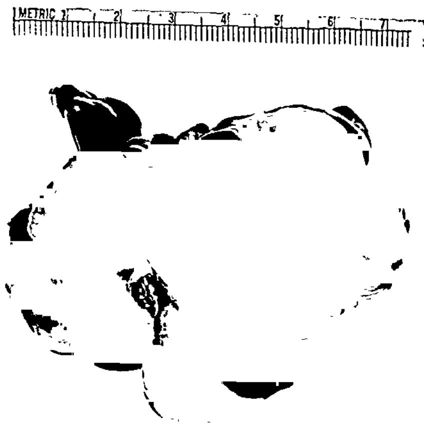


Fig 1—(F) Photograph of the excised specimen

patients with left atrial myxoma, a point of attachment of the tumor to the atrial septal wall was clearly visualized. Although angiocardiography of a patient with an atrial obstructing thrombus (ball-valve or pedunculated) has not been reported, it is probable that such a thrombus will produce similar roentgen findings Fortunately, exact differentiation is of no consequence since surgery should be considered for both the thrombus and the tumor

The cardiac intracavitary tumors are of two types. The myxoma is the most common and in fact comprises 50 per cent of all primary cardiac tumors It has been reported in patients from the age of 3 months to 68 years, the majority occurring between 30 and 60 years in equal sex distribution. The tumors are variable in size and may be so small as to cause no symptoms being discovered incidentally at autopsy Although there has been controversy as to whether the myxoma is a neoplasm or a thrombus, prevailing opinion holds that it is a benign tumor Strong evidence of the neoplastic nature of the myxoma is provided by a study reporting growth of a

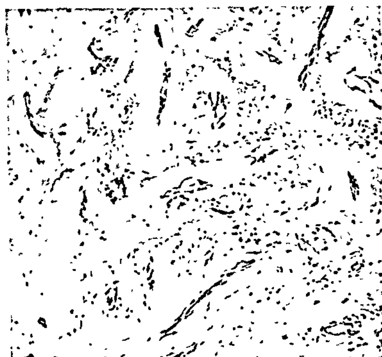


Fig 1—(G) Photomicrograph (× 100) of the tumor showing the characteristic myxomatous changes (Reproduced by permission of Dr Martin S Belle)

myxoma fragment in the mesenteric arteries and brain (Ringertz) This suggests that a myxoma is potentially malignant but none of the other reported cases showed lymphatic or hematogenous spread, local invasiveness or mitotic cells They are generally smooth, pedunculated or villous, whitish tumors of variable consistency (figs 1F and 2C) There may be areas of hemorrhage and occasional overlying thrombi. Microscopically, the tissue is rather poorly cellular with an endocardial covering Multinuclear and stellate cells and focal collections of plasma cells and lymphocytes have been noted (figs 1G, 2H, 3G and 4C) Cysts, bone and collagen deposition have also been described

The other variety of intracavitary cardiac tumor consists of sarcomas of all histologic types Although sarcomas are predominantly mural tumors, they are discussed here because the presenting symptoms are frequently due to intracavitary extension (fig. 5) Age and sex distribution are the same as for myxoma The sarcomas involve the right side of the heart more frequently and are polypoid in about 20 per cent. Unlike the myxomas, they involve the ventricles as often as the atria The clinical picture pro-

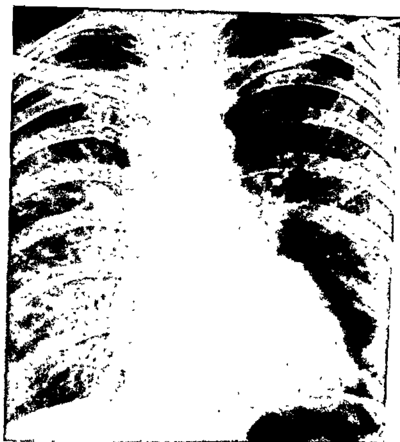


Fig 2—Left atrial myxoma in a 46 year old woman with sudden onset of heart failure ıd intermittent signs of mitral stenosis (A) Conventional teleoroentgenogram showing ılargement of the heart and prominence of the pulmonary artery segment

uced by the intracavitary cardiac sarcomas may resemble that due to myx-na, except for the frequent occurrence of hemopericardium, arrhythmias ıd the more common development of inferior and superior vena caval ɔstruction These tumors grow rapidly. Five cases have been diagnosed ıte mortem Approximately 25 per cent of Whorton's 100 cases showed no etastases at necropsy and of these there were 7 polypoid atrial tumors

Mural Tumors

Tumors involving the heart wall or valves, such as angiomas, hamartomas ıd nodular rhabdomyomas, have for the most part been reported as inci-ental autopsy findings A few strategically placed have caused arhythmias, terference with coronary blood flow and sudden death. Such a case was :ently described by Engle and Glenn.



Fig 2—(B) Lateral esophagram shows indentation of the esophagus by a large left atrium

Pericardial Tumors

The benign pericardial tumors are rare being only about one-fourth as frequent as benign tumors of the heart, per se Among the reported cases are teratomas fibromas, lipomas angiomas, cysts and leiomyofibromas Although these tumors usually arise from the myocardium or embryonic rests (fig 6), they expand into the pericardial cavity Many are discovered because of a chance x-ray demonstration of an unusual heart contour. In others, the sudden appearance of symptoms is due to the development of a hemorrhagic pericardial effusion This occurs almost as frequently in benign as in malignant pericardial tumors The malignant pericardial tumors pro-



Fig 2—(C) Frontal angiocardiogram shows a left atrial filling defect

duce a more rapid course, are associated more often with chest pain and dry cough and in one-third of the cases pulmonary metastases are seen. Electrocardiographic signs are of little help in either suggesting or for confirming the presence of a primary pericardial tumor since the changes usually reflect an effusion Diagnostic artificial pneumopericardium in the presence of an effusion has been strongly advocated by Mahaim Examination of pericardial fluid for tumor cells has led to the diagnosis in a few cases.

Diagnosis

The symptoms which may be produced by primary cardiac tumors are so much more frequently due to other lesions that the diagnosis will depend chiefly on a sharp awareness of the possibility. The left atrial tumor must be looked for in the patients who present symptoms and signs of obstruction of the lesser circulation. Signs of mitral stenosis not dating from birth in young children (Goldberg et al 1952), absence of cardiac difficulties until the onset of intractable heart failure, inconstancy of mitral murmurs, and episodes of syncope, cyanosis or dyspnea *without adequate explanation* except for the change in position are important clues Any of these findings should lead to angiocardiography. Some patients with left atrial tumors will

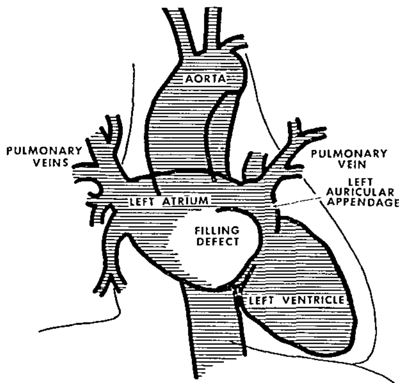


Fig 2—(D) Tracing of C

mimic rheumatic mitral stenosis so completely as to escape detection unless angiocardiography is used routinely in the evaluation of all patients being considered for mitral valvulotomy The need for exact preoperative diagnosis of a left atrial tumor is more than academic since successful surgery usually requires an open technic

Tumors of the right side of the heart will be found in patients who present signs of inflow stasis, which include dyspnea, orthopnea, dilated neck veins, facial edema, cyanosis, hepatomegaly, ascites, dependent edema, pleural effusion and increased venous pressure Preliminary diagnosis will include constrictive pericarditis, tricuspid stenosis and insufficiency, pericardial effusion, superior vena caval syndrome and chronic congestive heart failure The differential diagnosis of these conditions is often difficult even with the aid of a battery of laboratory examinations Angiocardiography, in this situation, will demonstrate the presence of a cardiac tumor as well as aid in the differentiation of the other conditions



FIG 2—(C) Frontal angiocardiogram shows a left atrial filling defect

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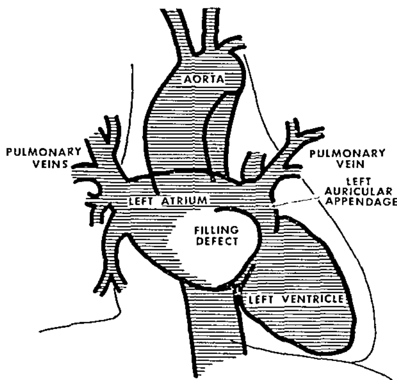


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Fig 2—(E) Lateral angiocardiogram also reveals the tumor in the left atrium attached to the atrial wall (For tracing, see facing page)

The diagnosis of primary pericardial tumors depends on the discovery of an unusual cardiac contour which is not readily explained (fig. 6A). There are no diagnostic clinical or laboratory criteria which will definitely differentiate with certainty pulmonary and mediastinal masses adjacent to the heart from intrapericardial tumors If the presence of a pericardial effusion can be established, examination of the fluid may lead to diagnosis of tumor In general, the diagnosis will await surgical exploration and biopsy (fig. 7). However, it is possible that angiocardiography by showing cardiovascular rotation and displacement (fig. 6B–E) recently demonstrated in a unique case of intrapericardial bronchogenic cyst and by Dabs and co-workers may provide a significant differential sign

Treatment

Exclusive of pericardial cysts, which have been removed on many occasions, successful surgery of benign intrapericardial tumors has been reported

Fig 2—(F) Tracing of E

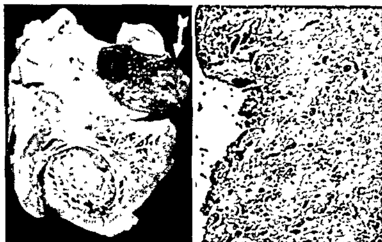


Fig 2—(G) Photograph of gross specimen showing the myxoma in the left atrium (arrow) (H) Photomicrograph (× 200) of the myxoma

Fig 3—Left atrial myxoma in a 53 year old woman (A) Frontal angiocardiogram, made in 1950, shows a huge left atrial tumor (B) Tracing of A (*below*)

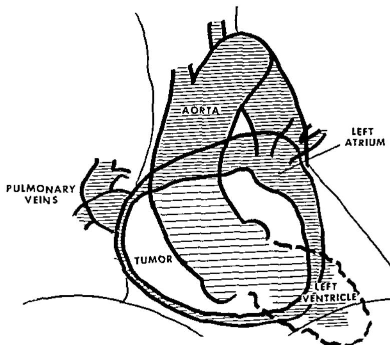


Fig 3—(C) Angiocardiogram, 3 years later, showed the tumor to be markedly enlarged (D) Tracing of C (*below*)

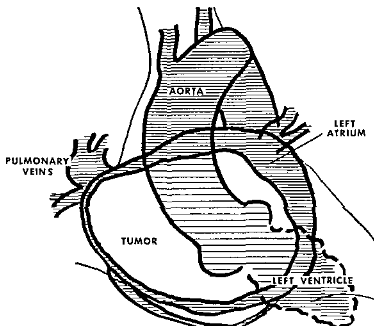




Fig 3—(E) Lateral view (1953) also shows the huge left atrial tumor.

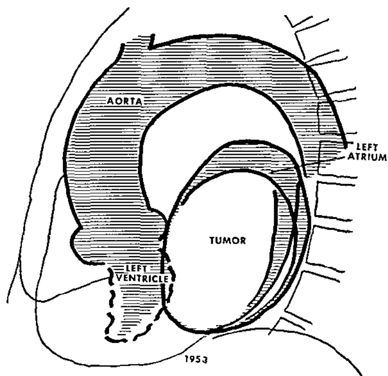


Fig 3—(F) Tracing of E

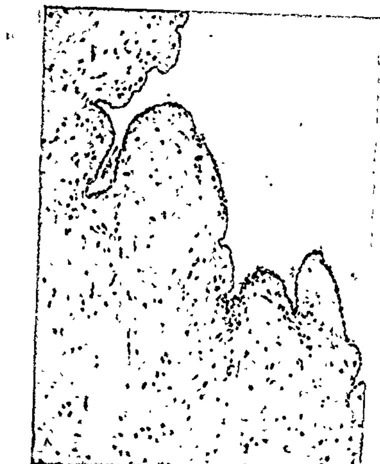


Fig 4—(C) Photomicrograph of the tumor (Reproduced from Goldberg et al [1952] with permission of the publisher)

ventricular fibrillation Bahnson succeeded in removing most of a right atrial myxoma and the patient lived for 24 days after operation. Death was due in part to obstruction of the inferior vena cava by residual tumor In two cases, attempted removal of the left atrial myxomas through the auricular appendage was unsuccessful; death occurred during surgery. One patient (fig 4) was explored but the small size of the auricular appendage prevented an attempt at removal of the tumor Surgery was not performed on Kirkeby and Lerens' patient. In addition, several myxomata have been found during surgery for mitral stenosis or constrictive pericarditis, but attempted removal at this time met with failure in all but one case (Fatti and Reid, 1958).

Clowes' patient was found to have a left atrial tumor during surgery for presumed rheumatic mitral stenosis. Surgical removal of the tumor was con-



Fig 5—Rhabdomyosarcoma causing marked obstruction of the pulmonary valve, right heart enlargement, right heart failure and cyanosis in a 44 year old woman (A) Frontal teleoroentgenogram showing enlargement of the heart The pulmonary vasculature is markedly diminished

sidered too hazardous Six months later, after several episodes of severe pulmonary edema, an open procedure with the use of a pump oxygenerator to bypass heart and lungs, was carried out The patient, however, died six hours after operation

The first successful removal of a left atrial myxoma was reported to Goldberg and Steinberg (1955) by Crafoord as follows "I can inform you that after exact anatomical diagnosis due to selective cardioangiography, on July 16, 1954, we operated on a case of pseudomyxoma of the left atrium, the size of a small orange, with the aid of complete bypass with extracorporeal oxygenation and circulation produced by our own pump-oxygenerator The blood was shunted from the cavae to the aorta through the left subclavian artery During the 28 minutes of exclusion of the heart from the circulation and the intracardiac manipulations the heart was in a state of

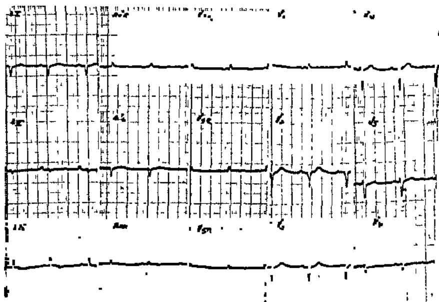


Fig 5—(B) Electrocardiogram showing right ventricular hypertrophy in rhabdomyosarcoma



Fig 5—(C) Photograph showing the massive pedunculated tumor obstructing the pulmonary artery and valves

Fig 5—(D) Photomicrograph showing rhabdomyosarcoma of the heart (Reproduced through the courtesy of Mannix and Lukash)



Fig 5—(D) *See legend, facing page*

Fig 6—Intrapericardial bronchogenic cyst in an asymptomatic 3 year old girl (A) Frontal teleoroentgenogram showing a huge cardiac silhouette



Fig. 6—(B) Angiocardiogram showing medial displacement of the superior vena cava by a huge mass



Fig 6—(C) Angiocardiogram reveals marked rotation of the right atrium, ventricle, pulmonary artery and right branch



Fig 6—(D) the left atrium appears to be in its proper position



Fig 6—(E) The left ventricle, and ascending aorta, however, are markedly rotated indicating that the pericardial tumor is distorting the right atrium, pulmonary artery and ventricle and displacing the left ventricle



Fig 6—(F) Photograph showing the huge lobulated intrapericardial tumor

Fig 6—(G) On section, the tumor appeared cystic



Fig 6—(H) X-ray of the gross specimen revealed scattered areas of calcification

ventricular fibrillation intentionally brought about by electrical stimulation in order to facilitate the extracorporeal circulation and the actual technical procedure within the heart After closure of a maximal wide incision in the left atrium, the heart was electrically defibrillated The postoperative period was somewhat disturbed by a slight rise in both nonprotein rest urea in the blood and a moderate elevation in the bilirubin This healed otherwise without complications and the patient is now considered completely recovered Before the operation, the patient had the usual symptoms of paroxysmal mitral occlusion and mitral stenosis which now no longer are present"

Soon after, Scannell (1956) reported the removal of a left atrial myoma with hypothermia Hopkins (1956), Hanlon (1956), Bahnson (1957), Robertson (1957), Fatti (1958). Gerbode (1958), Coates and Drake (1958) and Ellis (two cases [1958]) have successfully removed left atrial myxomas A right atrial myxoma removal utilizing hypothermia was accomplished by Krèilková and co-workers in 1958 Scannell in 1958 also reported the removal of a fibrosarcoma from the right atrium in a 7 year old child who presented with a bloody pericardial effusion Exploratory operation without interruption of circulation revealed an intramural and intra-atrial mass



Fig 6—(I) Photomicrograph (× 240) of intrapericardial bronchogenic cyst revealed bronchial epithelium

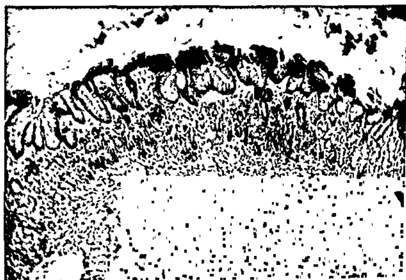


Fig 6—(J) Another section (× 240) showed gastric mucosa



Fig 7—Hemangioma of the left ventricle in a 25 year old man (A) Frontal angiocardiogram showing a large nonopacified left ventricular mass (arrow)

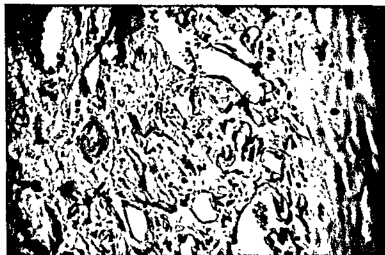


Fig 7—(B) Photomicrograph of the biopsy specimen shows a sclerosing hemangioma attached to heart muscle (arrow) (Courtesy of Dr Harold A Lyons)

which was excised. A rent in the atrium was repaired by a flap of atria pendage. The patient made an uneventful recovery but returned two w later with *tachycardia*, *increased* venous pressure and symptoms sugge recurrent cardiac tamponade. Re-exploration failed to show perica fluid although the heart was enlarged. Resection of the pericardium leaving a "large window" resulted in recovery and this has persisted fo most two years.

Summary

Modern open heart surgery has *made* possible *successful* removal of diac tumors. Most of the cardiac myxomas have been diagnosed after atrial exploration for operative relief of mitral stenosis. Usually, this caused *abandonment of the operation and made necessary a second op*tion following recuperation Often, this is a serious handicap for a pat already disabled with advanced hemodynamic difficulties Accordin *preoperative diagnosis is essential and can be achieved by angiocard*raphy. Admittedly the selection of the patient for angiocardiography in case of tricuspid or mitral stenosis is difficult. Awareness of the possibi *is probably the most important factor in the diagnosis. Finally, angioca*ography by disclosing rotation and displacement of the heart within pericardium will indicate the presence of an intrapericardial tumor.

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CHAPTER 19

Metastatic Tumors in the Chest

By DAVID M SPAIN, M D

ANY DISCUSSION OF INTRATHORACIC METASTATIC CARCINOMA can only serve a useful purpose to the extent that it facilitates differential diagnosis for the purpose of eliminating needless procedures, prolongs life or alleviates suffering. The purpose is also served if, from studies on metastatic carcinoma, a better basic comprehension of the malignant process is obtained

Secondary carcinoma within the chest may involve pleural surfaces, pulmonary parenchyma, bronchial walls, hilar and mediastinal lymph nodes, mediastinal tissues, pericardium and heart Advent into the chest by malignant tumors may be gained through the blood stream, lymphatic channels or by contiguous invasion The origin may be from both sarcoma and carcinoma Of all of the intrathoracic sites of involvement with secondary carcinoma, that of the lung is of the most clinical importance and occurs with the greatest frequency It is generally estimated that about 30 per cent of all fatal cases of malignant tumors will metastasize to the lungs Carcinoma of the kidney will end with metastases in the lungs in almost 3 out of every 4 cases It is not surprising that the lung is such a frequent site of metastasis because where tumor cells are dislodged from other primary sites directly into the blood stream or into lymphatic vessels, eventually primary filtration must take place in the lungs From a clinical point of view, because of the easy recognition of shadows on the chest roentgenogram, the lungs are frequently the first site for the detection of carcinoma that originates elsewhere in the body

The incidence of metastases to the lung from malignancies of various organs is listed in table 1 [1, 11, 13]

DIFFUSE LYMPHANGITIC METASTASES

Of particular interest for a variety of reasons is that form of secondary carcinoma in the lung described as diffuse lymphangitic metastases.[2, 10, 14] This pattern of metastatic carcinoma may present itself with a variety of clinical syndromes, or on occasion may remain clinically dormant The origin may be from primary carcinoma of many different sites Not infrequently, the primary tumor produces no detectable clinical picture. In an autopsy group of 30 such cases studied by me, the stomach was the most frequent site of origin The distribution of these sites of origin for lymph-

TABLE 1—*Incidence of Metastases to the Lung from Malignancies of Various Organs*

Primary Growth	Metastases to the Lung (%)		
Renal carcinoma	75	40	65
Osteosarcoma	75	—	—
Fibrosarcoma and liposarcoma	—	54 5	—
Chorio-epithelioma	75	—	—
Carcinoma of thyroid	65	60	—
Malignant melanoma	60	62 5	—
Carcinoma of breast	55	62	77.2
Oropharyngeal carcinoma	30	22 (approx)	—
Esophageal carcinoma	20	25	—
Carcinoma of stomach	20	16 8	32 8
Carcinoma of liver	20	15 (approx)	—
Carcinoma of pancreas	20	25	34
Carcinoma of colon	—	21 2	37.2
Uterine malignancy	15	43.7	—
Ovarian carcinoma	10	12	34
Author	Willis	Turner and Jaffe	Abrams et al
No of necropsies	500	1,303	1,000

TABLE 2—*Primary Sites of Origin for Diffuse Lymphangitic Metastases in the Lungs*

(30 autopsied cases)

Primary Site	No of Cases	Primary Site	No of cases
Stomach	11	Prostate	2
Bronchus	5	Pancreas	2
Colon and rectum	4	Kidney	1
Breast	4	Bile Duct (Intrahepatic)	1

TABLE 3—*Prominent Initial Symptoms in Diffuse Lymphangitic Carcinoma of Lung*

(30 cases)

Symptoms	No of Cases	Symptoms	No of Cases
Dyspnea	18	Orthopnea	4
Cough	9	Chest pain	3
Wheeze	5	Ankle edema	2
Cyanosis	5	No symptoms at any time	5

angitic metastases in the lung is presented in table 2. It may be noted that 5 of the 30 patients never had symptoms referable to the chest. Pleural effusion was present in 23 of the 30 cases and was bilateral on 17 occasions. ... This ... e free

from blood

Several interesting clinical syndromes have been associated with these ... sub- ... ur-

ticularly in the past when the pattern produced in the lungs by this form of metastases was not so widely recognized, definitive extensive surgical procedures were attempted on the primary tumors unknowingly in the presence of such metastases In these cases the x-ray pictures of the lungs were usually interpreted as nonspecific fibrosis (table 3)

Because the primary tumors may remain silent in the presence of such metastases and because the spread in the lungs produces diffusely linear and finely nodular x-ray shadows, confusion or difficulty has existed in differentiating this pattern of metastases from such conditions as hematogenous miliary tuberculosis, finely nodular silicosis, nodular densities associated with mitral stenosis and other bilateral diffuse and finely nodular lesions.

The nature of the pulmonary involvement provides some insight to the manner of production of these protean clinical manifestations and to certain fine characteristics of the x-ray picture which may aid in differential diagnosis It is postulated that metastases first involve the hilar and mediastinal lymph nodes to such an extent that the flow of lymph in the usual direction is blocked When this occurs there is retrograde extension or permeation of tumor from the hilar region through the peribronchial and perivascular lymph channels towards the periphery of the lung Eventually, there is a diffuse involvement of the lungs On the x-ray picture this often resembles, particularly on close inspection, a fish net because at the points of junction of the linear shadows usually small nodules are present This *combination of fine nodules connected by linear streaks often helps to differentiate* this condition from hematogenous miliary tuberculosis and the other entities in which the nodules are discrete without connecting linear streaks In a number of instances, however, the hilar and mediastinal lymph node involvement is scant It is then difficult to account for the spread of the cancer cells throughout the lungs on the basis of retrograde lymphatic permeation For this reason, it has been claimed by some that the first step in the process is a widespread tumor embolization of the terminal pulmonary vessels These tumor emboli then involve the peripheral perivascular and perbronchial lymphatic channels, and then by following the normal flow of lymph from the periphery to the hilar region, infiltrate the entire lung Acute or subacute dyspnea often associated with a wheeze is a consequence of the peribronchial involvement and associated obstructive emphysema Where this type of involvement has predominated, patients have presented themselves with a clinical picture of acute paroxysmal dyspnea and wheeze that has at times been mistaken for an atypical form of asthma (see figs 1 and 2)

Subacute cor pulmonale with or without congestive failure runs a rapid clinical course from a period of several weeks to months during which marked dyspnea is a prominent clinical manifestation along with cyanosis

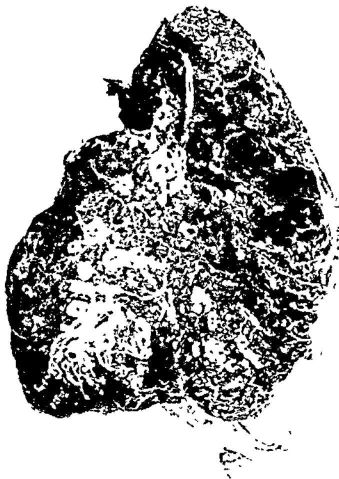


Fig 1—Gross specimen of lung showing extensive tumor infiltration around blood vessels and bronchi This tumor is primarily in the lymphatic spaces and originated from a primary carcinoma of the stomach The patient had dyspnea and pulmonary hypertension

The pulmonary hypertension that develops in this situation appears to be related to three lesions. These are organizing arterial thrombi, sometimes associated with presence of tumor emboli, tumor emboli alone blocking smaller arteries and arterioles and finally an obliterative endarteritis. In one collected group of 78 cases with diffuse lymphatic carcinomatosis of the lungs, hypertrophy of the right ventricle of the heart was present 10 times [10] Pulmonary hypertension may terminate fatally within a matter of weeks Awareness and early recognition of this clinical syndrome that



Fig 2—Photomicrograph showing carcinoma in the peribronchial lymphatic vessels secondary to primary carcinoma of the breast This was clinically confused with radiation fibrosis

results from lymphangitic carcinomatosis may direct one's attention to a silent primary tumor and save the patient numerous needless and discomforting diagnostic procedures When these metastases are derived from such primary tumors as breast carcinoma and prostatic carcinoma, the use of certain hormones or chemotherapeutic agents may produce temporary resolution of these metastases with corresponding diminution in the x-ray shadows and functional disability In other instances, radiation has produced similar results The presence of such metastases in the lungs is almost always indicative of widespread involvement elsewhere

Thus, the peribronchial involvement produces the picture related to obstructive emphysema Vascular involvement may produce subacute cor

pulmonale and alveolar wall involvement may produce the syndrome of alveolar-capillary block. *These patterns may* occur together, or any one may predominate.

Solitary Peripheral Metastasis

A single peripheral metastatic nodule or mass in the lung from an extrathoracic primary malignant peoplasm occurs much less frequently than the characteristic multiple nodular metastases. This occurrence may lead to considerable difficulty particularly where there are inadequate signs or symptoms to direct attention to the primary site. Needless pulmonary resections have been performed in the mistaken belief that such a nodule or mass was of primary bronchogenic origin. It should, however, be borne in mind that removal of such an isolated metastatic mass either subsequent to, or even preceding the removal of the extrathoracic primary tumor, has on more than one occasion resulted in surprisingly long periods of survival Thus, even with the knowledge that such an isolated nodule is metastatic, serious consideration must always be given to the possibility of resection It is currently recognized that these do not always have a hopeless outlook. The major difficulty remains in the distinction from a resectable bronchogenic carcinoma. Details of the roentgenographic differentiation of these lesions have been discussed in Chapter 7.

One group of patients with solitary metastatic nodules on whom varying degrees of lung resection were performed consisted of 18 metastatic carcinomas and 11 metastatic sarcomas[6] Of the 18 cases with carcinoma, 17 survived at least one year following resection, 9 survived at least 2 years, 6 survived at least 3 years and 2 survived at least 5 years. In a collective review of 264 cases in which pulmonary resection was performed, 3 7 per cent of the cases with metastatic carcinoma and 15 per cent of the cases with metastatic sarcoma survived over five years. In some of these, the primary site was only recognized as being elsewhere than in the lung after resection revealed a characteristic microscopic morphology that identified the actual primary site. Particularly characteristic of such situations is the clear cell carcinoma of the kidney which metastasizes as a solitary mass to the lungs more than any other tumor (see fig. 3). In some cases where adenocarcinoma is found in the periphery of the lung even after resection, it is possible to remain unaware of the fact that the tumor is metastatic until post-mortem examination or the later development of clear cut symptoms reveals the primary site.[4, 7, 9]

Metastatic Involvement of a Major Bronchus

It has been an axiom that if a neoplasm produces hemoptysis or bronchial obstruction, it is primary in the lung. As with almost all such generalizations exceptions occur. One of the least frequent types of metastases to



Fig 3—Gross specimen of lung showing a single large circumscribed metastatic mass in the upper lobe that was secondary to a clear cell carcinoma of the kidney This was mistaken for a primary bronchogenic carcinoma

the lung are those that involve the wall and lumen of a major bronchus This infrequent involvement of a major bronchus may be secondary to compression or invasion from cancer containing hilar and mediastinal lymph nodes A much more rare occurrence is metastases to the wall of a bronchus via the arterial system When the bronchial wall and lumen are involved with secondary carcinoma, the x-ray picture and bronchoscopic examination are indistinguishable from that seen with primary bronchogenic carcinoma The symptoms, signs and complications consisting of cough, hemoptysis, wheeze, obstructive pneumonitis and lymph node en-



Fig 4—Gross picture of a close up view of an open bronchus that shows the protrusion of a metastatic nodule of carcinoma The primary tumor was in the liver The patient presented himself with hemoptysis and was thought to have a primary bronchogenic carcinoma

largement are also similar Only if biopsy of the bronchial lesion produces cells specifically characteristic for a neoplasm arising from another site can the distinction be made. I have seen such cases in which occult primary tumors have been present in the liver, thyroid, prostate, kidney and colon (see figure 4). Other reported sites have been breast, testes, melanoma of skin and gall bladder [5, 9, 12] Some of these have had attempts at definitive resections for the lung tumors Clearly, the results obtained are uniformly poor as contrasted with solitary peripheral metastases Despite this, thoracotomy is often justified because proof that the tumor is not primary in the lung may be considerably delayed

Atypical Forms of Metastases

A variety of metastases might be considered under this common grouping of atypical. These would be "benign" metastasis, long-lasting metastasis, spontaneously regressive metastasis and intra-alveolar implantations from a primary or secondary tumor in the lung Consideration might also be given at this point to the difficult distinction between bilateral nodular metastasis and the uncommon development of bilateral multiple primary bronchiolargenic tumors and pulmonary adenomatosis of multicentric origin (see figures 5 and 6).

Benign metastasis refers primarily to two conditions—endometriosis of the lungs and trophoblastic emboli *"Vicarious menstruation"* has been as-



Fig 5—Classic multinodular metastases in lung originating from a primary tumor in the prostate

cribed to extragenital endometriosis An authenticated case with surgical material in which a pulmonary mass contained endometrium with a decidual reaction has recently been reported [8] Hematogenous metastasis following surgical procedures best explains this situation Undoubtedly, small emboli reach the lung frequently during delivery or surgical procedures on the pregnant uterus, but only rarely do these implants of trophoblastic tissue survive

Long-lasting metastases in the lungs have been reported on numerous occasions. The observation of such metastases was one of the original pieces of evidence that host factors might play an important role in the biologic



Fig 6—Photomicrograph of primary multicentric alveolar or terminal bronchiolar carcinoma that was mistaken for metastases to the lung

behavior of a neoplasm I have seen proven metastasis from a melanoma in the lung and pleura remain stable with the patient in "good" health for a period of eight years In this case, the primary site had been established In the absence of a known primary, this can be a troublesome diagnostic problem Long-lasting metastasis in the absence of specific therapy casts doubt on the claims of some therapists.

Documented cases of spontaneous disappearance of pulmonary metastasis have also been recorded. The most noteworthy example is metastasis from choriocarcinoma. Because of this infrequent development and because of variations in survival with pulmonary metastasis, some caution should be exercised in determining prognosis

Intra-alveolar implantation at many scattered points of tumor spreading through the bronchial tree from a metastasis or a solitary primary in the lung may simulate hematogenous metastasis from an extrapulmonary site or be indistinguishable from a multicentric carcinoma of alveolar origin.

Lung Cancer Associated with Other Primary Neoplasms

At times, primary bronchogenic carcinoma exists in combination with primary malignant tumors arising in other sites These other tumors may have preceded, arisen simultaneously or appeared subsequent to the detection of the lung tumors. This combination of multiple primary cancers will probably increase as survival rates improve This will become an increasing problem. The implications of this from a diagnostic point of view are intriguing. In an individual who has had a primary carcinoma arising

from an extrathoracic site, and who has had definitive treatment, the subsequent appearance of a solitary nodule in the lung may not necessarily indicate metastasis from this original primary site It may in reality be a primary bronchogenic carcinoma The chances of a solitary nodule in the lung being metastatic in such a situation are about one out of three This must always be borne in mind In equivocal situations exploratory thoracotomy is indicated since there are no sure radiographic signs to distinguish a metastatic nodule from a primary tumor In one series of 2,562 consecutive cases of bronchogenic carcinoma, there were 81 other primaries present This is an incidence of 3 2 per cent Particularly prominent among the sites for other associated primary malignant tumors are the regions of the head and neck (lip, alveolar ridge, tongue, floor of mouth and larynx) This may be related to common etiologic factors In 64 cases of associated primary malignant tumors in other sites, the extrathoracic neoplasm was synchronous 24 times and metachronous 40 times [3]

Metastases to the Pericardium and Heart

A study by the Harvard Cancer Commission based on 4,375 post-mortem examinations in which cancer was present revealed 146 cases (3 4 per cent) with metastases to the pericardium and heart These represented blood borne or lymphogenous metastases and not direct infiltration from tumors of the mediastinum or lungs In another study based on 1,000 autopsies the frequency of such metastases was 3 5 per cent. Of the 146 cases, carcinoma accounted for 102 and sarcoma for 26, while 18 arose from a primary melanoma Breast, lung and stomach were the most frequent sites of primary carcinoma that metastasized to the heart This probably only reflects the higher incidence of these tumors Of all the tumors, only melanoma appears to have a special predilection for myocardial metastases out of proportion to its primary incidence

The involvement usually consists of discrete varying sized nodules that may extend to the pericardial or endocardial surfaces In over one-third of the cases the pericardium is involved usually with the production of a serosanguineous effusion Much less frequently, the valves become involved When the valves or endocardial surfaces are penetrated by tumor, further dissemination of cancer ensues by embolization from these sites Of the sarcoma group, lymphoma in particular involves the myocardium

The clinical manifestations are varied and may consist of cardiac failure, angina, changing murmurs, dyspnea, arrhythmias, venous obstruction and pericardial effusion A post-mortem examination performed by me on an individual with extensive myocardial metastases from a primary bronchogenic carcinoma had an acute clinical onset that was interpreted as an acute myocardial infarct that occurred during the strain of lifting a heavy object

The tumors may produce arrhythmias by involving atrial coronary arteries with subsequent atrial infarction, by direct atrial wall destruction and by involvement of sympathetic and parasympathetic fibers. Varied patterns of heart block may be induced by tumor involvement of the sino-auricular node and atrioventricular conduction system.

Diagnosis is usually not established during life, and at present there is no treatment which can significantly alter the outcome.

Summary

Metastasis to the lungs may exist in various patterns. Each pattern presents its individual diagnostic and therapeutic problems. These patterns are bilateral multiple nodules, diffuse miliary nodules, lymphangitic carcinomatosis, single peripheral nodule and extension into a major bronchial wall. Of these, single peripheral nodules are sometimes amenable to relatively long survival following resection.

Metastases to the heart and pericardium are much less frequent, more difficult to diagnose and usually not amenable to even short-term palliation

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CHAPTER 20

Radiation Therapy and Radioisotopes in Tumors of the Chest

By BERNARD ROSWIT, M D.

INTRODUCTION

DESPITE DRAMATIC ADVANCES IN RESECTIONAL SURGERY for intrathoracic neoplasms, the overall survival rate is still less than 10 per cent It does not appear realistic to expect much improvement in the relatively small proportion of cases suitable for surgical resection The chemotherapy approach has been unfruitful in terms of salvage for these individuals and there is little prospect for improvement in the near future

Radiation therapy, therefore, must shoulder the principal burden of responsibility for the large body of surgically inoperable patients because it offers relief from distress and disability in the majority of the cases and may *sometimes extend the period of productive and comfortable life*

The recent introduction of high energy therapeutic radiation, advances in radiation technology, precisional dosimetry and better understanding of radiation reactions in critical tissues have made it feasible to give more effective dosage to deep-seated tumors with minimal local and systemic reactions

These benefits of modern radiation therapy have recently prompted a reappraisal of its role in the treatment of operable and borderline operable cases as an important adjunct to surgery (preoperative or postoperative), or even as a substitute for surgical treatment in selected favorable cases, particularly those with bronchial or esophageal carcinoma Preliminary clinical studies, still sharply limited in time and in scope, already suggest the possibility of greater aid and comfort to individuals with intrathoracic cancer, through this combined effort

*It appears to us, however, that too many practitioners, recalling the se*vere radiation reactions which were commonplace in the past decade, are still denying their less advanced patients (unsuitable for surgery) the advantages of modern radiation therapy

It is our purpose in this chapter to discuss briefly the technology of therapeutic radiation, the system of treatment planning and the principles which should govern the selection of cases referred to the radiologist This discussion is based on our experience with the treatment of nearly 2,000 patients with tumors of the chest and on the best efforts of our colleagues in other radiation clinics, both here and abroad

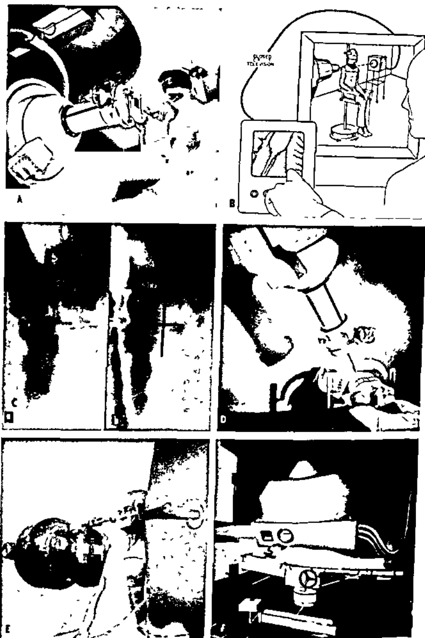


Fig 1—The technology of radiation therapy in chest tumors (A) Million volt x-ray machine delivering rotational therapy to patient with high cervical esophageal carcinoma. Note the immobilization technics utilizing plaster shell and cranial device to prevent a "geometric miss" (B) Closed-video system for constant surveillance of barium-filled esopha- ... at all times (C) Radio-

what occurs when a slight error in angulation (only 3 degrees) is introduced The center

General Principles

Technology of Radiation Therapy

The technical achievements of thoracic surgery in the past five years have been both striking and enduring, promising greater benefits and fewer surgical risks to patients with chest tumors. Not so widely heralded are parallel advances in the technology of tumor therapy with ionizing radiation. Radiologists, physicists, engineers and biologists have been quietly pooling their several skills and resources to improve the attack on deep-seated, radioresponsive neoplasms, particularly those within the thorax.

Of great significance, among these radiologic advances, is the recent development and wider availability of supervoltage x-ray generators and Cobalt-60 therapy equipment (fig. 1). In comparison with conventional beam radiation (200 to 400 kilovolts), supervoltage beams (1,000 to 4,000 kilovolts) provide more penetrating x-rays with a greater percentage tumor dose, minimal damage to skin and bone, little radiation sickness and leukopenia and greater facility for more radical treatment. The earlier cancer patient is thus offered a better chance for cure and improved palliative benefits. However, for palliative treatment in later cases, supervoltage radiation is not essential. For such individuals the skill and experience of the radiologist may be more important than the voltage, especially if other radiologic advances of recent years are utilized to maximum advantage.

Our associates in radiologic physics have provided exquisite tools for accurate dosimetry in human tissues and have helped to design more precisional methods for the planning and delivery of the prescribed dosage. They have offered us a number of versatile radioisotopes for introduction into thoracic tumors by a variety of ingenious technics. The slender prospects for clinical success in this area have not discouraged them.

Special equipment generating x-ray and electron beams from 4 to 35 million volts is becoming available in Europe and in the United States (fig. 1). It is not unlikely that these beams will find a strategic place in the treatment of chest cancers in the next several years. Evidence is already available to suggest that results in the thorax may thus be further improved while minimizing the side effects of radiation, both local and systemic.

Fig. 1—*Continued*

of the beam now strikes the spinal cord while the tumor is off on the outer edge of the beam and receives only about 50 per cent of the dose. (From Roswit, B.: A new roentgen ray beam director for precision radiation therapy. Am. J. Roentgenol. *65*: 115, 1951, courtesy of Charles C Thomas.) (D) Arrangement for precise delivery of million volt x-rays to bronchogenic carcinoma. Note precision beam directors on machine head and on patient's chest. (E) Cobalt 60 therapy apparatus delivering x-ray beam equivalent to that from 2 million volt x-ray generator. (F) 35 million volt betatron for megavoltage therapy of deep-seated tumors. (Printed by permission of Brown, Boveri & Co., Ltd., Switzerland.)

Methodology of Treatment Planning

Just as in the surgery of cancer therapy, there can be no excuse for a level of radiation technic which falls short of the highest achievement possible. An orderly system of treatment planning has been developed to assure the patient of a treatment plan ideally suited to his individual needs.

The margins of the tumor are defined as accurately as possible, utilizing physical, surgical, endoscopic and radiologic technics (fig. 2). These include the use of contrast media, fluoroscopy, angiography and three-dimensional tomography. The surgeon is importuned to mark the margins of nonresectable disease with metal clips or gold seeds in patients being explored.

An accurate horizontal cross section of the patient's body in the treatment plane is graphically reconstructed, showing the body contour, the tumor volume and correct spacial relationships of important normal structures. This reconstruction is derived from a tracing of a quick-drying plaster bandage impression and the anatomic landmarks from a standard cross section atlas. We have developed tomography in the transverse or horizontal plane to replace the atlas because this unique radiologic method offers us a living anatomic cross section or third dimension of the patient under consideration. More precise knowledge of the location and volume of the tumor as well as displaced normal structures is thus immediately available.

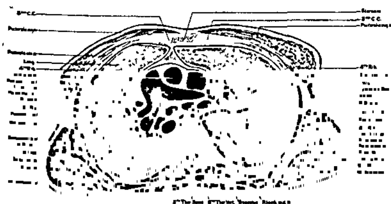
An optimum dose-time formula is then prescribed in roentgens (or rads) and over-all treatment days, with the upper limits of permissible dosage to critical normal structures clearly stated This prescription is highly indi-



Fig 2—Methodology of radiotherapy in chest tumors. (A) A plaster body contour is being made through the central horizontal plane of the tumor. This will provide the basis for an anatomic reconstruction of the body cross-section and evolvement of an individualized treatment plan



Fig 2—(B) The plaster reproduction of the body contour is being traced on grid-ruled planning sheet for imposition of the anatomic parts and the tumor



C

Fig 2—(C) Anatomic cross section illustrating the normal anatomy in this plane (Printed by permission of Charles Thomas, from "Symington Cross Section Atlas")

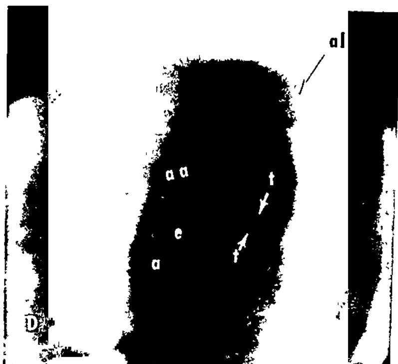


Fig 2—(D) The transverse tomograph of the same patient in the same plane illustrating the true reproduction of the living anatomic section in our own patient. Note the tumor mass compressing the bronchus (t), the atelectatic lung (a, l), the barium-filled esophagus (e), the aorta (a) and the aortic arch (aa)

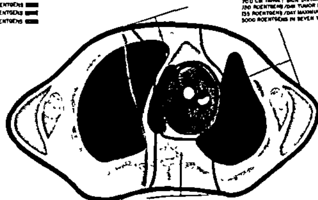


Fig 2—(E) This is the final treatment plan evolved from an orderly planning system, illustrating the isodose pattern and the cross firing portals designed by the physicist and the radiologist



Fig 2—
mobilizing plaster shell, the beam directors and the back-pointing device In the background is seen the rotational table occasionally employed for treating this lesion

vidualized and is modified throughout the treatment course, as dictated by the patient's response The physicist assists in the choice of the number and angulation of treatment portals, the ideal radiation energy, the precise dosimetry and other important technical factors The final plan may involve a pair of simple anteroposterior portals, a complex system of several cross firing beams or a rotational technic The rotational or "rotisserie" method simulates an infinite number of beams cross firing the tumor, while sparing normal intervening tissues

Now the patient is readied for treatment but there is still the risk of a "geometric miss" Absolute verification of the accuracy of beam alignment is achieved by radiographic means, using the therapy beam itself Furthermore, the patient is immobilized in a plaster jacket or other mechanical restraint for each treatment setting His tumor may even be visualized on a closed video circuit throughout the treatment Special devices for precise beam alignment are available including angle directors, pin and arc units, back pointers and photocells, and transit dosimetry (fig 2)

As treatment progresses, the patient is regularly examined in the radiation clinic and careful assays are made of the clinical and radiologic response by the radiologist and practitioner Their skilled judgment and experience will govern the limits of the cumulative dose

Selection of Patients

In most cases, it becomes immediately obvious whether the candidate is entirely unsuitable for x-ray therapy or whether irradiation is feasible for a radical or palliative goal. In some instances, the radiologist will need to marshal his best clinical judgment and experience to make the right decision. In case of doubt, radiation should always be tried for a brief period—for about two weeks, or 2,000 roentgens (tumor dose). If he begins to improve and takes the treatment well, the course may be carried to a palliative level of 3,000 to 4,000 roentgens or even to the maximum radical dose of 5,000 to 6,000 roentgens in four to six weeks. Most radiologists are agreed that the higher the dose the better the result—whether the goal be palliation or improved survival—but acceptable limits of tissue tolerance must never be exceeded. Experience has shown that, with hyperintensive, overagressive therapy, especially in the thorax, the end results deteriorate.

In general, a patient with a malignant tumor in the chest is accepted or rejected for radiation treatment on the basis of (1) the histologic entity and radiosensitivity of the neoplasm, (2) the extent of the disease, (3) the patient's general condition, (4) the clinical needs of the individual or (5) his psychologic needs.

Histology and Radiosensitivity

The most important single factor which defines the acceptability of a patient for radiation treatment is the histology of the neoplasm. In our radiation clinic, no intrathoracic tumor is treated without histologic or cytologic verification of malignant disease, including type and degree of differentiation (except in extraordinary circumstances such as superior vena cava compression). The so-called "test of irradiation" is no substitute for a biopsy in the diagnosis of a suspected mediastinal or parenchymal tumor. The delay is inexcusable and the response may be unreliable. When in doubt, operate. We recall an asymptomatic young male with large hilar nodes who received about 2,000 roentgens (tumor dose) as a "diagnostic test" in lieu of thoracotomy. We were convinced that malignant lymphoma or some other radiosensitive lesion could be ruled out and persuaded the surgeon to explore the thorax. Three large, discrete, lymphosarcomatous nodes were trimly excised and the patient has been in good health for 10 years.

Radiosensitivity does not necessarily connote radiocurability. Among the most radiosensitive tumors to be encountered in the thorax are the oat cell tumors of the bronchus, the thoracic neuroblastomas and the rare malignant lymphomas which appear to have their origin in the chest; yet, the curability rate is depressingly low because of the inexorable development of remote metastases. These disease entities will be further discussed as specific clinical problems.

Generally speaking, the more undifferentiated is a tumor, the better its radiation response, but the basic histologic type remains the principal determinant of radiosensitivity. For example, a rhabdomyosarcoma of the heart, even if anaplastic, will be resistant, while a well differentiated epidermoid carcinoma of the bronchus can be eradicated

The following is a reasonable order of relative sensitivity (1) very radiosensitive lesions—such as the oat cell tumor, neuroblastoma, Wilm's tumor and seminoma, Ewing's tumor and malignant lymphoma, (2) radioresponsive lesions—such as carcinoma of the bronchus, trachea and esophagus, and metastases from breast, thyroid, kidney and ovary, (3) radioresistant lesions—notably the soft tissue sarcomas, affecting the heart, pericardium, and pleura and metastases from stomach, colon, pancreas, central nervous system, prostate, melanomas and osteogenic sarcomas It is well to remember, however, that one cannot always predict response from the microscopic view We have occasionally been surprised by the sensitivity of individual tumors of known radioresistance, especially since the advent of supervoltage radiation and more radical dosage

Extent of Disease

The larger the tumor volume to be irradiated the more limited is the dose tolerance of intervening normal structures The larger the tumor the smaller the possibility of benefit Massive lesions tend to become anoxic, necrotic and radioresistant A necrotizing neoplasm with cavitary changes, without ready access to a bronchus is generally not suitable for treatment by any radiation method and such patients generally do poorly Therefore, in lesions of predictable radiosensitivity—treat sooner rather than later

Involvement of the pleura with or without effusion only infrequently yields to external beam therapy. Paralysis of the diaphragm and of the vocal cords is rarely reversed On the other hand, endobronchial obstruction and atelectasis secondary to pressure by enlarged lymph nodes is frequently relieved. This is probably one of our most important palliative contributions In the presence of remote metastases, rigorous treatment of the primary chest lesion cannot be justified unless it is giving rise to intractable pain or discomfort and is of a radioresponsive histologic type

General Condition

In the practice of our radiation clinic, we do not regard any patient with a grossly symptomatic intrathoracic tumor as "hopeless" and unsuitable for consideration of a trial of palliative radiotherapy. We reject only those who are extremely cachectic or present an enormous lesion, with infection, necrosis or massive pleural effusion The admission of such subjects for treatment is not calculated to improve our statistical survival records, but the palliative benefits in individual cases has encouraged us to pursue this

sonable dose levels, reactions in these tissues seem to be well tolerated and rarely does one see intractable residual discomfort or disability. In some clinics, where an effort has been made to explore hyperintensive and more aggressive tumor dosage (in the range of 6,000 to 8,000 roentgens) severe changes in these tissues have been noted

It is the tolerance of the normal lung itself which remains today the critical limiting factor that must be considered in any realistic effort to destroy a local lesion and its regional nodes. At present dose levels (4,000 to 6,000 roentgens in 4 to 6 weeks) radiation fibrosis is observed on x-ray but the patient is usually not aware of this event, especially if it involves the upper lobes. We believe that the minimum dose for this reaction is about 4,000 roentgens in four weeks when large portals are employed. One occasionally sees late and severe radiation fibrosis and this could be disabling when a very large area is involved. Even in such cases there have been successful attempts at resection of the troublesome tissue.

In our own experience with nearly 2,000 irradiated chest neoplasms, we have seen only 6 deaths due to radiation pneumonitis. In such cases there is a striking individual variation in sensitivity, but overaggresive daily tumor doses (>250 roentgens), high cumulative total dose (>6,500 roentgens) and very large portals play significant roles The larger the daily dose, the cumulative dose and the irradiated volume, the more likely is the lung to respond *with an acute, alarming clinical syndrome—the "wet" reaction* This may begin shortly after the completion of the course of treatment and is characterized by a diffuse pneumonitis largely limited to the irradiated volume The patient experiences a dry cough, chest pain, high fever, marked dyspnea and malaise Respiratory function studies reveal the findings of an alveolar-capillary block syndrome. In such instances he should have prompt and complete bed rest, oxygen and antibiotic therapy. The corticosteroids may be helpful. The syndrome may reverse itself in a period of two to three weeks, go on to consolidation and death, or heal with dense fibrosis.

To minimize the risk of these reactions, (1) we avoid excessive daily or total tumor dose when a large volume is treated, (2) employ precise tumor localization technics, (3) develop a treatment plan which delivers maximum dosage to the tumor and reduces radiation to the lung, (4) verify accuracy of beam alignment, (5) effectively immobilize the patient, (6) use maximum beam collimation and (7) respect the minimum tolerance levels of critical thoracic tissues

A serious effort is being made, in human subjects with cancer of the lung and other epidermoid lesions, to enhance or potentiate the effect of radiation on the tumor through chemotherapeutic agents and high pressure oxygen (Mitchell, Sanger). The preliminary trials are promising, suggesting the possibility that, in selected cases with limited disease, the cancerocidal dose may be reduced to a level consistent with survival of normal lung tissue.

SPECIFIC CLINICAL PROBLEMS

Bronchogenic Carcinoma

Never before in the history of our nation has there been such intense concern over the menace of a single malignant disease. In American males over 45 who smoke heavily, bronchial cancer is assuming an epidemic quality. Nearly 27,000 new cases were reported last year in this country The ominous nature of the disease has not been altered; the majority of patients are inoperable when first seen, the yield of resectable cases remains painfully small in spite of steady improvement in diagnostic methods, and the absolute surgical cure rate is at best about 7 out of 100

It is apparent, therefore, that the clinician and the radiologist face an obligation to provide nonsurgical treatment for most patients with bronchogenic carcinoma. Radiation treatment can play a significant role in assisting patients with this disease at various stages, from the relatively early lesion in some patients unsuitable for surgery, to the patient with remote metastases and a relatively short life expectancy

Chemotherapy has yet failed to yield a single agent or combination of agents which can favorably influence survival time or even match the palliative benefits of modern roentgen therapy Furthermore, these drugs are all employed at high risk to the integrity of the patient's blood-forming organs. As the search goes on for a "wonder drug" for patients yet to come, increased emphasis should be placed on radiotherapy as an adjunct to surgery for the greater benefit of patients now at hand (see Chapter 21).

Distant Metastases The patient with severe pain and disability from a lytic skeletal metastasis can expect a reasonable chance for prompt relief from a short intensive course of conventional roentgen therapy—about 200 to 300 roentgens daily for 10 treatments Not infrequently reconstruction of bony architecture will be observed If a fracture impends in a large limb bone, we prefer to "nail" the fragments and then proceed with radiation

An individual with involvement of the central nervous system is usually desperately in need of help because of the profound functional and behavioral disturbances This complication, observed in about 15 per cent of our cases, creates a severe strain on family and community resources because of the continuous nursing care it demands Nothing is more gratifying than the frequent and lasting relief radiation can offer from intractable headaches, confusion and disorientation, cranial nerve dysfunction and paraplegia. In patients with anaplastic lesions, these results are particularly striking Because of the hazard of sudden edema, it is wise to begin treatment of brain or spinal cord with smaller daily tumor doses (100 to 150 roentgens) and carry the total dose to 3,000 to 4,000 roentgens A variety of other common metastatic lesions are worth treating if they are symptomatic, such as



Fig 3—Radiation response of bronchogenic carcinoma. Here are 3 patients with proven bronchial carcinoma, inoperable, with atelectatic lung segments and involved hilar and mediastinal nodes (x-rays on the left) (A, C and E) In each instance note the dramatic radiologic response, with relief of endobronchial obstruction and aeration of the appropriate lung (B, D and F) This was accomplished with dose levels from 3,000 to 5,000 roentgens in 3 to 6 weeks (x-rays on the right).

painful hepatic enlargement, massive skin nodules and uncomfortable peripheral nodes.

Advanced Primary Lesions What can the radiologist offer the grossly symptomatic patients with an advanced primary lesion involving regional nodes and contiguous structures—with or without remote metastases The extent of malignant disease generally precludes any attempt at a realistic effort to improve survival time Nevertheless, they are entitled to the same basic humanitarian and medical considerations as other patients with chronic, progressive and debilitating lung disease External beam therapy, with conventional or high energy radiation, is the best way to give relief. The portals are large and the dosage modest, usually less than 4,000 roentgens

Palliative radiation should be seriously considered for all symptomatic cases except in the presence of marked cachexia, massive chest disease necrotizing, cavitating or infected lesions and intractable pleural or pericardial effusions The latter respond better to radioactive colloidal materials or nitrogen mustard.

In more than 50 per cent of cases treated, palliative roentgen therapy gives *symptomatic* relief from productive cough, hemoptysis dyspnea, orthopnea, dysphagia and chest pain Improvement may be noted in the first two weeks of treatment, but for more lasting benefit, treatment should be carried through for four to six weeks for a tumor dose of about 4,000 roentgens In practice, dosage is adjusted to meet the patient's symptomatic needs and the limits of his local and total tolerance *Objective* evidence of satisfactory response may be observed in the aeration of atelectatic lobes, clearing of obstructive pneumonitis, regression of pulmonary lesion and shrinkage of involved lymph nodes Indeed, the most important advantage of effective radiation is in re-establishing bronchial drainage because the symptomatology of distal suppuration dominates and wastes the patient's life Supervoltage radiation is not essential for these cases, but it is surely an advantage, because of minimal radiation reactions and ease of administration

The clinical syndrome associated with compression of the superior vena cava is today nearly always the result of invasion of the prevascular and right paratracheal lymph nodes and/or the great vessel itself by anaplastic bronchial cancer. Despite the ominous clinical picture, 75 per cent of these cases, in our experience, have responded well to radiotherapy. When we delivered a tumor dose of 3,000 to 4,000 roentgens in 4 to 5 weeks, there was no recurrence of the syndrome before death, for periods up to a year after treatment Nitrogen mustard is not a substitute for radiation in these cases because it is far more toxic and the remissions of very short duration However, we do employ nitrogen mustard in a single intravenous dose of 0 4 mg per kilo of body weight as a prelude to x-ray treatment because the

initial response to nitrogen mustard is more prompt, and definitive radiation can then be started a week later with full dosage schedule. Nitrogen mustard is further employed by us for patients in whom radiation is no longer feasible or effective. Occasionally, such patients will respond well enough to become suitable candidates for definitive radiation treatment

Until the availability of supervoltage therapy, we had little success in controlling the intractable pain associated with the Pancoast syndrome, arising from invasion of the apex of the lung, the thoracic cage, the spine and the brachial plexus. Effective dosage can now be delivered in this area and a few long-term survivals have been achieved in spite of gross involvement of bones and nerves (Haas)

In this apparently hopeless group of patients, which most radiologists get to treat, the principal objective of radiotherapy is to relieve distress and disability. Its effect should be assayed only by symptomatic and objective benefits and not by the parameter of survival. Nevertheless, it is of interest that even in this advanced stage of disease a modest improvement in life span is reported as well as an occasional long-term cure (Leddy, Craver, Kutz, Brooks, Guttmann, etc.). In a recent survey we conducted, the majority of therapeutic radiologists questioned had well documented records of such cures One of our own patients is illustrated in figure 4



Fig 4—A 10 year radiation cure for nonresectable proven carcinoma of the lung (A) This was a nonresectable Pancoast-type lesion invading and destroying the thoracic cage and involving the cervical plexus Attempt at surgery was unsuccessful The diagnosis of adeno-epidermoid carcinoma was established in this grossly symptomatic 60 year old male veteran (B) More than 10 years after radiation therapy (3,500 roentgens in 3 weeks). The lesion remains controlled and the radiograph is negative for disease. The patient is in perfect health and has continued his occupation

Limited Primary Lesions: What shall we do for the patient who at first presents a tumor of limited local extent but definitely not operable, or of borderline operability, or rejected as nonresectable after thoracotomy, or locally recurrent. Many of these patients are in fairly good general condition without evidence of distant metastases and may have relatively few complaints It is our impression that, in this country, such individuals are generally not referred for radiation therapy until their disease becomes far more advanced and they become "sick enough to need radiation" On a national scale this group may represent as much as one-third of the 27,000 new cases reported last year.

The only present hope for improving the over-all salvage rate rests on radical irradiation of the local lesion under optimum conditions in this allegedly unfavorable group of individuals, as early as possible in the course of their disease. It would be unrealistic to expect a striking improvement in the cure rate from such an effort, but we cannot afford to look for "pie-in-the-sky." Gains would be measured in terms of enhancement of average survival time. Considering the large number of individuals involved, this objective alone would be well worthwhile Apparently inoperable lesions may become operable. The surgeon would have "a second look" Further, it would be safe to predict that some long-term cures would be recorded

What is the evidence that localized bronchial cancer, unsuitable for resection, is a radiovulnerable lesion? There are already several retroscopic observations to lend support to an affirmative opinion (1) the radiosensitivity of single lesions—primary and metastatic, notably in undifferentiated and epidermoid tumors, but seen in all histologic types, in our experience with more than 1000 cases, (2) post-mortem studies revealing complete eradication of proven primary lesions and regional nodes as well (Churchill, Haas, Guttmann, Bromley, Smithers, etc), (3) obliteration of the chest lesion in 44 per cent of a group of operable and inoperable patients subjected to preoperative radical irradiation and later explored An additional 14 per cent showed only degenerate tumor cells present (Bromley and Szur), (4) well documented reports of long-term cures after radiation for inoperable local disease (Smithers, Burnett, Euphret, Craver, Leddy, Felton, etc), (5) *significant improval in average survival time from several radiation* clinics, both here and abroad (Smithers, Brooks, Kutz Guttmann, Boland etc)

A randomized prospective study of careful experimental design should be undertaken to provide statistically acceptable data to answer the question as to whether modern radiation therapy can improve survival for inoperable bronchial cancer of limited extent

Can supervoltage radiation offer longer survival than conventional radiation in this group of cases? Preliminary evidence suggests it can (Kutz,

Watson, Haas, Guttmann, Hare, Boland, etc.). For example, in a recent study at the Christie Hospital in Manchester, small primary bronchial carcinomas (inoperable) were submitted for radical treatment by means of 250 to 500 kilovolt therapy and a 4 million volt linear accelerator. At the end of two years, more than twice as many of the high energy treated cases were alive (Boland).

Operable Lesions. What can the radiologist do for patients with operable lesions, applying the radiologic advances of the last few years to optimum advantage? So long as radiologists rarely get to treat such cases, it remains impossible to state fully and confidently the curative potential of radiotherapy. It is generally agreed that Stage I epidermoid carcinoma in other anatomic sites (oral cavity, larynx, cervix, etc.) is a radiocurable disease. There is little reason to believe that Stage I epidermoid carcinoma of the bronchus will behave differently under radiation management.

Of considerable interest is a recent report from London describing a unique group study of radiation therapy in proven cases of operable bronchial cancer Of 25 patients, 5 have lived from six to nine years There were no peripheral lesions and all patients had the mediastinum treated, although none had clinical evidence of mediastinal nodes prior to radiation. The x-ray treatment was highly individualized but all received conventional radiation, with dose levels of 5,000 to 5,500 roentgens for the squamous carcinomas and 4,000 to 4,500 roentgens for the undifferentiated lesion in seven to eight weeks None of the patients in this series died of radiation pneumonitis When these authors compared their data with the surgical rate at two monthly intervals, the radiotherapy figures appeared better than those for surgery for the first two years and much the same thereafter. Of further interest are 3 additional operable cases (2 were anaplastic) referred to the radiologist in this study group All three patients have lived more than five years after radiotherapy without apparent disease (Smart and Hilton)

The true potential of radiotherapy for cure can only be ascertained from the randomization of operable proven cases (histologically or cytologically) between surgical resection and supervoltage radiation. In the meantime, the clinician will continue to refer his operable cases to the thoracic surgeon, reserving for the radiologist those who refuse surgery, or are rejected by the surgeon because they cannot withstand the operation, or present anaplastic lesions which are rarely cured by surgery.

Esophageal Carcinoma

Carcinoma of the esophagus is still a grim disease, with an absolute survival rate of less than 1 per cent There is little reason to expect much improvement in this figure through earlier diagnosis or more radical surgery.

More than one-half of the patients with this insidious disease are already nonresectable when first seen and thoracic surgery for the rest is as daring as it can be. To improve the probability for greater salvage, we shall have to look to high energy radiation, in combination with surgery or radiotherapy alone in selected operable cases such as those with upper third and middle third lesions. As in bronchogenic carcinoma, it is unrealistic to expect a dramatic improvement in the cure rate through such an approach, but the gains in palliation and in cumulative survival time may be very real indeed

The clinician confronted with the need for a wise therapeutic decision in a particular patient must first gain an appreciation of the advantages and the limitations of both the surgical and radiologic methods He must integrate a number of critical factors to assay the chance for cure or palliation by either method. These factors include the age and general condition of the patient, the site, stage, type and histology of the lesion, and the mortality and the morbidity rate proffered by the surgeon and the radiologist

Upper Esophagus On the basis of our experience with 263 treated cases and a careful assay of the reports from other tumor centers (Buschke, Adams and Salzman, Burnett and Moore, Pettit, Sweet, Smithers, Haas, etc) we would select supervoltage radiotherapy for apparently operable lesions in the cervical esophagus and the upper fourth of the thoracic esophagus About 17 per cent of lesions are found in this anatomic zone

In skilled hands, a five year cure rate of about 17 per cent can be achieved with radiation treatment in the cervical esophagus—the area of highest surgical mortality and rare cure (Jacobsson) Our only long radiation survivals (1 for 10 years, another for 14 years) were inoperable patients with high lesions Here the radiologist can deliver cancerocidal doses with negligible morbidity There is little intervening lung and the tumor and nodes are closer to the surface Any radiation fibrosis produced here is no real clinical problem Indeed, a death due to such treatment would be extraordinary.

These advantages of radiation treatment are not appreciated by most surgeons As late as 1956, Wangensteen stated, in a monograph for the physician, sponsored by the American Cancer Society, that "despite the magnitude of the procedure, operation has become the order of the day in most clinics in this country In a few areas, there is still a remnant of enthusiasm for roentgen ray treatment" *This distinguished surgeon readily agrees,* however, that "the results of surgery for cancer of the upper thoracic esophagus have been so disappointing and the operative mortality has been so high that surgeons are more willing to have their roentgenologist colleagues continue to explore the possibilities of ablation of such cancer by irradiation " Operative mortality in this area is between 40 and 50 per cent Some surgeons have invited their radiologic colleagues to join them in a *combined*

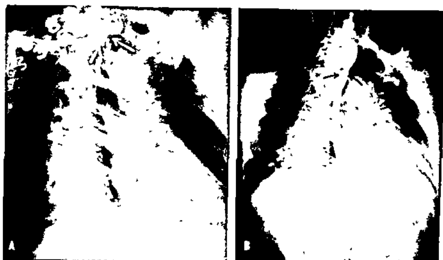


Fig 5—A 14 year radiation control of esophageal carcinoma. (A) Note the completely obstructing lesion in the upper third of the esophagus at the thoracic inlet Biopsy showed epidermoid carcinoma in this 55 year old male veteran A tumor dose of 5,600 roentgens was delivered with conventional therapy through 5 cross firing portals 14 years ago in our radiation clinic (B) Esophagram illustrating the previous site of the lesion with complete restoration of normal function for 14 years with repeated biopsies consistently negative for cancer cells A new lesion appeared last year below this site and gastrostomy was followed by the patient's demise A post-mortem examination was not available

effort to cope with these formidable tumors because "radiation has made the upper lesions tend to a more favorable prognosis" (Adams and Salzman).

Middle Thoracic Esophagus Carcinomas located in the middle half of the thoracic esophagus comprise about 70 per cent of the cases. In a careful and authoritative comparison of therapeutic results on a world-wide basis, Buschke concludes that the five year results obtained by surgery and radiotherapy are in the same range He emphasizes, moreover, that the radiologic series includes many cases that would have been rejected even for exploration by the surgeons.

Autopsy studies of patients who die of progressing disease outside of the esophagus or of other causes have demonstrated the absence of disease in the treated portion of the esophagus more frequently than would be consistent with chance alone. In Watson's series, for example, 5 out of 7 autopsies showed no evidence of recurrence in the esophagus (3 of these died of cardiac failure) Smithers, in his group of 32 completely treated patients observed 3 instances in which at post-mortem no evidence of residual tumor or ulceration was found, in addition to the 3 patients who were free from symptoms for more than 5 years. In 4 additional cases local ulceration but no viable cancer was found at post-mortem; 6 more patients died without return of symptoms These data would suggest that in 16 of the 32 adequately treated cases, the primary lesion was controlled

How then should one integrate the selection factors to make a wise choice of treatment? Clearly, radiotherapy should have increasing preference with increasing age Sweet reports that the mortality in patients over 65 years of age was four times that of patients under 45 years of age On the other hand, neither age nor general condition (except advanced cachexia) is a serious deterrent to effective radiation therapy Further, the presence of cardiopulmonary disease at the outset does not seriously influence the therapy; nor is the patient likely to expect as great a hazard of death from cardiac disease, pulmonary embolism, hemorrhage, infection, pulmonary insufficiency or anastomotic stricture as with surgery

Patients with highly anaplastic lesions are best spared a radical surgical procedure because their probability for cure is minimal In such cases, however, maximum palliation benefits can be gained by radiotherapy As in carcinoma of the lung, the trend is presently toward ionizing radiation for highly undifferentiated lesions, especially since recent reports of provocation to spread through the surgical procedure

According to Buschke, the gross x-ray appearance of the lesion is a dependable lead to prognosis and to choice of treatment For example, he would consider the constricting circular lesion somewhat more favorable for surgery because they are associated with minimal lymph node involvement and can be more easily excised Even if radiation is selected and fails, surgery is still possible The exophytic lesion, on the other hand, is usually unfavorable for cure by any means because of early spread through lymphatic and regional nodes Yet, they are really more radioresponsive than the first group

The superficial mucosal cancers are the least suitable type for surgery because they are prone to rapid and widespread lymphatic extension, remote metastasis and local perforation They are seldom curable when recognized by either surgery or radiation treatment It is, therefore, doubtful whether one is justified in subjecting these patients to the greater discomfort associated with surgical removal

The possibility of perforation of the esophageal wall during radiation is an old objection raised by surgeons and clinicians, but it is not one which the radiologist takes seriously because he encounters it in only a very small number of his treated cases, and the types which perforate might be expected to do so without radiation. In these cases (which represent the large ulcerating and disintegrating tumors) surgery will likewise fail Adams and Salzman of the Lahey Clinic have been surprised at the occurrence of so few incidents of perforation and hemorrhage in their series of 40 supervoltage treated cases.

Lowest Fourth of Thoracic Esophagus In this anatomic site are found about 13 per cent of epidermoid esophageal carcinomas Surgery should have preference in this area because the surgical cure can be achieved here in

about 15 per cent of the resectable cases, with a primary surgical mortality of only 11 per cent (Sweet). Further, with surgical exploration, one can recognize and remove regional nodes below the diaphragm Radiation treatment, to be effective in these important lymph nodes, must include a very large volume of tissue, with the tolerance of the stomach as a limiting dosage factor (about 4,000 roentgens). Supervoltage radiation is essential in this area if x-ray is selected. If the histology proves to be adenocarcinoma, then surgery would most certainly be the method of choice.

General Discussion

Surgical and radiologic failures are mainly due to the early spread throughout the regional lymphatic nodes. There are deposits in the intramural lymph nodes along the esophagus and in the para-esophageal and mediastinal lymph nodes. Microscopic cancer consistently seen at the line of anastomosis led to recurrence and breakdown in many cases at the Lahey Clinic (Adams and Salzman) We share this experience.

These profoundly depressing facts have prompted these authors to adopt a combined program of radical surgery and postoperative supervoltage radiation A tumor dose of about 6,000 roentgens in 6 weeks is delivered, when feasible, to the entire esophagus and its lymphatic vessels, using 2 million volt radiation. This portal includes the lymphatic nodes of the periesophageal, cervical, supraclavicular and infraclavicular areas. The trend in their results, reported in June 1959, has justified these workers to continue the combined approach They conclude that "combined resection and supervoltage radiotherapy is of distinct value and we are continuing to treat all cases we possibly can with this combined treatment"

Ravitch and his colleagues, reporting at the 1952 meeting of the American Association of Thoracic Surgery, stated that "results of extirpation of carcinoma of the esophagus to date have been so discouraging as to raise serious questions concerning the value of the direct attack." When only palliative results can be expected, radiation therapy should have preference over any type of surgical procedure We have been able to restore and maintain oral feeding in at least 50 per cent of the patients treated. Nielsen reports that complete or nearly complete primary freedom from symptoms (almost normal deglutition and radiologic improvement of the passage) was obtained in 117 out of 174 patients treated, or in two-thirds of the total number or four-fifths of the adequately treated patients This result is even more impressive when one considers that about one-third of these cases had enormous lesions more than 10 cm in length on the radiograph. In many instances, patients are able to swallow up to the time of death, which, in most cases, is due to metastases and cachexia.

Is there any reason to hope for better surgical salvage in the upper and

middle thoracic lesions through radical preoperative radiation? There is a keen interest in this question at the Memorial Hospital in New York because, in the history of this institution, there could be found only 2 survivors from surgical treatment of this lesion. Accordingly, from 1956 to 1958, 20 patients with upper and middle thoracic lesions received preoperative irradiation for a tissue dose of 6,000 roentgens in 6 weeks, utilizing a rotational cobalt beam. Within six weeks after completion of the radiation course, 11 of these individuals were found to be resectable Their lesions had regressed markedly, when compared with preoperative evidence from radiographs and esophagoscopy Six of these 11 operated cases had either no tumor at all or a small residual nidus In only two instances was tumor found to invade through the esophageal wall Most striking was the absence of regional nodes and in only 2 cases were there distant nodes visualized

During the same period, 13 private patients were admitted to the hospital with lesions similar to those in the irradiated group Of these private cases, none were irradiated and only 5 proved to be resectable All of these patients had extension of tumor through the esophageal wall and 4 had histologically positive regional nodes This study, which will continue, suggests that supervoltage preoperative irradiation can improve the resectability rate eradicate the primary lesion, limit invasion through the esophageal wall, control regional nodes and improve the probability for survival All of these benefits were accomplished without clinical or radiologic evidence of pneumonitis and without complicating the surgical procedure in any way Survival records will soon be published by this group (Cliffton, E , Goodner J T and Bronstein, E).

We employ a polyethylene tube for forced feeding to support the patient during radiation therapy This is feasible in most cases, but if not, a temporary gastrostomy is sometimes advised However, a gastrostomy is no substitute [illegible]
without c[illegible]
certainly [illegible]
a state of "withering undelight," for eating, apart from being a necessity, is the greatest of living pleasures This gone, life is not worth living "

Rare Primary Malignant Tumors

Carcinoma of the Trachea In the trachea the adenocarcinomas and the squamous cell carcinomas are about equally divided, representing nearly all the rare malignant lesions found in this structure The basal cell cancers account for the rest. As in cancer of the esophagus, this tumor has a tendency to spread widely in an axial manner invading the local lymphatics. Dramatic operative procedures have been conceived using reconstructive procedures and plastic replacements We would urge that such patients first

be explored and a surgical effort be made for cure with radiation as an adjunct Only 1 of our 6 cases has survived radiation therapy alone and he still appears to have persistent disease in spite of a cumulative tumor dose well over 10,000 roentgens (in two courses)

Thymic Tumors: The interpretation and classification of the host of lesions which have been called "thymomas" is exceedingly complex and beyond the scope of this section on therapeutics. Nevertheless, the therapeutic radiologist has an important place in the management of these tumors, especially if they become "malignant" or are associated with myasthenia gravis A thymic tumor must be called "malignant" if it extends, invades and implants neighboring tissues, eventually destroying its human host, unless checked. We find them on routine chest radiography and less often from symptoms of thoracic pain or superior mediastinal obstruction.

Although the primary treatment of thymic tumors is by surgery, adjunct radiation treatment—generally preoperative, sometimes postoperative—is essential Supervoltage x-rays are preferred because of minimal skin reaction, higher depth dose, less leukopenia and sparing of normal pulmonary and mediastinal tissues A tumor dose of 4,000 roentgens in four weeks is the dose objective, beginning with a small dose of 50 to 100 roentgens if myasthenia is present. The treatment course may be fraught with unusual complications such as high fever, atypical pulmonary infections, myasthenia crises, mediastinitis and pericarditis Close day by day management of the patient by the medical and radiologic team is mandatory.

Response to irradiation is assayed by roentgen evidence of regression of the mass and by improvement in myasthenia Thymectomy may be contemplated about two months after radiotherapy, if it is indicated, but slow improvement in the myasthenia may delay the surgical procedure Jones, Keynes and Harper have treated 18 cases and 13 are alive from one to five years Three patients are entirely free from complaints from two and one-half to four and one-half years, while useful improvement has been gained in nine other cases Five individuals died from irreversible myasthenia (all within 18 months of treatments) These authors warn that the ultimate prognosis must remain guarded because relapse of myasthenia may occur after a complete remission of even three years.

Irradiation of the nonmalignant thymus in myasthenia gravis has been difficult to evaluate because of the variability of spontaneous remissions in myasthenia We agree with Jones that it should be reserved for older patients no longer responsive to neostigmine. It is of further interest that preoperative irradiation followed by thymectomy appears to enhance control of myasthenia and survival

Malignant Tumors of the Pleura: These rare neoplasms may be local or diffuse—the local lesions treated surgically and the diffuse tumor irradiated, with little profit in either case.

Tumors of the Heart and Pericardium In a single lifetime no clinic is likely to encounter more than a handful of such cases They are nearly all advanced when first seen and not usually amenable to surgical resection, nor do they respond well to conventional radiation treatment because they are sarcomatous Nevertheless, when confronted with such a problem, the radiologist may treat with supervoltage radiation to restrain the tumor growth The tolerance of the normal cardiac and pericardial tissues is unusually high, but the intervening pulmonary tissue will restrict the dose to less than 6,000 roentgens, especially because huge treatment portals are generally needed.

Other Mediastinal Tumors Of the rare soft-tissue sarcomas which are found in the chest none are responsive to ionizing radiation except the liposarcomas, and hardly ever is one of these lesions controlled because of widespread metastases

When a malignant lymphoma appears to have its origin in the chest and is well localized, we believe in making an effort for long-term survival through surgical resection, if feasible, or radiation therapy Indeed, a localized focus of Hodgkin's disease, lymphosarcoma or reticulum cell sarcoma may be controlled with a tumor dose of 3,000 to 4,000 roentgens in three to five weeks

The neuroblastomas will be discussed in the section on pediatric tumors

Metastatic Tumors

Invasion of the pulmonary fields or mediastinum by metastatic neoplasms is a common and formidable clinical problem Except for carcinoma of the thyroid, breast and prostate, and lymphomas and leukemias, which may also be treated by other modalities, all other sarcomas and carcinomas secondary in the lungs can be handled according to the principles we have already outlined for primary pulmonary tumors Some tumors may grow slowly and produce almost no symptoms If their histology is of a known *radioresistant* type, then radiation therapy may be withheld However, the *radiosensitive lesions, even if asymptomatic, should be treated to a tumor* dose of 2,000 roentgens to the whole chest if bilaterally distributed, irradiating just one lung field at a time These lesions include seminoma, lymphosarcoma, neuroblastoma, Ewing's tumor, Wilm's tumor, etc We have seen a few 5 year remissions in patients so treated Hemoptysis frequently responds to radiation therapy as well as cough and productive expectoration (see Chapter 22)

Patients with *radioresponsive* primary lesions such as carcinoma of the breast, esophagus, bronchus, cervix, oral cavity, thyroid, etc deserve every consideration when they present themselves with symptomatic lung infiltrates or mediastinal nodes Even when asymptomatic, we think that radiation should be attempted in a "holding effort' because the onset of extreme

dyspnea and gross pulmonary disability may thus be delayed. Such lesions should therefore be treated as early as possible and to dose levels of about 3,000 to 4,000 roentgens to the local area

In a situation in which a single metastatic lesion appears in the lung several years after the primary has been removed by surgery or destroyed by radiation, we would undertake to heavily irradiate this focus unless the patient would agree to a lobar resection

We have a special interest in malignant lymphomas involving the lung, based upon our experience with nearly 1,000 patients with these systemic diseases This lesion responds exceedingly well and deserves more aggressive therapy than is usually accorded to metastatic lung disease. In one instance we have seen a local remission of more than 10 years after 4,000 roentgens to the right upper lung field. Huge excavating pulmonary infiltrates have healed for several years and no recurrences were noted in the local site. Pulmonary Hodgkin's is a serious complication but can be well managed by radiation therapy, with help from the newer alkylating agents, as well as nitrogen mustard (see Chapter 13)

The response of thyroid cancer to external radiation is varied and unpredictable The pulmonary lesions frequently respond to x-ray therapy, but if they are capable of concentrating iodine, then I^{131} therapy should be first treated In our experience the alveolar and follicular tumors are most likely to acquire the I^{131} The only limiting factor to aggressive radioiodine dosage is damage to the blood-forming organs.

The objective of treatment for secondary lung tumors is to relieve symptoms, maintain morale, increase the period of a useful life and occasionally prolong life It should be emphasized that in the individual patient favorable remissions to treatment is sometimes unpredictable. We are therefore justified in pursuing a more optimistic and more aggressive therapeutic approach in these chronically ill patients

Tumors of Childhood

General Considerations In the management of pediatric neoplasms, the role of radiotherapy is principally palliative It assists the surgeon, the pediatrician and the chemotherapist at all stages in the disease. In at least one major cancer of childhood—Wilm's tumor—radiation treatments add greatly to the chance for cure as an adjunct to surgery for the primary lesion.

There are several important differences between radiotherapy in adults and in children that need to be discussed. The normal tissues of children are distinctly more radiosensitive, with little margin between tumor dose and tolerance dose. For example, the blood cell picture may show sudden and profound effects, especially when a large chest volume is exposed. The skin of the chest wall and abdomen seems to be more sensitive than the same tissue elsewhere in the child or in the adult. The growing ends of bones and

the endocrine organs require special protection to minimize late effects on the skeleton and other development of the growing child The closer proximity to the skin of the essential deep organs gives them a higher selective dosage, with earlier complications of cystitis, gastritis, proctitis, and enteritis. Systemic effects are similar to those encountered in adults It is of particular interest that after the age of 10 the radiation tolerance rapidly approaches that of a mature person.

In pediatric therapy, supervoltage radiation is distinctly helpful, because it spares the skin and bone and limits the scattered radiation to normal tissues As a consequence, leukopenia and radiation sickness are sharply reduced, treatment planning becomes simpler and treatment becomes safer Nevertheless, the daily dosage is maintained at a lower level than adults and a five day week is employed Lead shielding is generously used and the child's body effectively immobilized, in a plaster shell, if necessary The lungs, especially, should be spared excessive radiation, because the child tolerates radiation pneumonitis very badly

Specific Tumor Problems Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma are infrequently seen in childhood In spite of a gratifying immediate response to radiation, these children rarely survive more than a year or two after diagnosis

Neuroblastomas arising in the chest and pelvis have a much better prognosis than those primary in the adrenal, especially when treated early and effectively with roentgen therapy Metastasis to the lungs from a primary lesion elsewhere is virtually unknown

Wilm's tumor, metastatic to the lungs, is strikingly radiosensitive and deserves a real effort at long-term control even when massive deposits are seen in the radiograph After treatment of the entire lung field (one hemithorax at a time) remissions have lasted as long as five years, with dose levels of only 2,000 to 2,500 roentgens

Even the metastatic osteogenic sarcomas are worth treating because they may sometimes respond surprisingly well

For several years, most pediatricians and radiologists in this country have abandoned the practice of routinely irradiating an enlarged thymic shadow when laryngeal stridor was present. It is now recognized that there are striking variations in thymic size in different children and in different phases of respiration If the diagnosis of thymic hyperplasia becomes well established and stridor becomes chronic and severe, then radiation treatment is the best choice, with a dose of 50 to 75 roentgens repeated twice in one week.

Radioisotope Therapy

Hundreds of ingenious investigations have been undertaken in the past 10 years in an attempt to deliver effective doses of ionizing radiation to

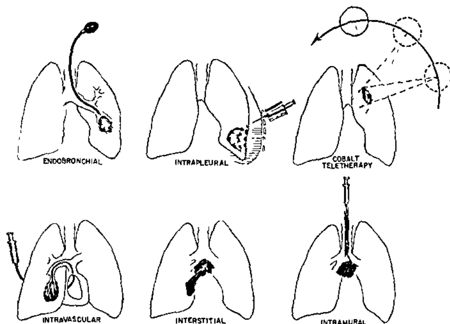


Fig 6—Radioisotope therapy in lung cancer Illustration of several methods for delivering selective radioactivity into the bronchus, lung, tumor and lymph nodes.

pulmonary neoplasms, primary and metastatic, utilizing a variety of radioactive isotopes. These versatile agents have been introduced by intravenous, intra-arterial, interstitial, transbronchial and pleural routes (fig. 6) They include radioisotopes of gold, phosphorus, silver, zinc, yttrium, iridium and cobalt.

From a practical viewpoint, the fruits of these investigations have not been striking, except for the use of radioiodine in thyroid metastases, intrapleural administration of radiocolloids for effusions, interstitial therapy with gold and iridium and the external beam therapy with cobalt Nevertheless, many palliative benefits have been gained, when assessed in terms of relief from distress and occasional prolongation of useful and comfortable life. The principal obstacles encountered in the exploitation of radioisotopes for lung cancer therapy include (a) inability to promptly localize the nuclear agent in high concentration in the diseased tissues and (b) the intolerance of critical radiosensitive tissues such as the bloodforming organs and the lungs It is especially in bronchogenic carcinoma that *every* avenue of research needs to be explored to find a radioisotope adjunct to external beam therapy in the nonresectable patient which will be truly effective and clinically safe for the patient and his community.

Transbronchial delivery of colloidal radiogold has been accomplished, irradiating lung parenchyma at high therapeutic levels without bone marrow

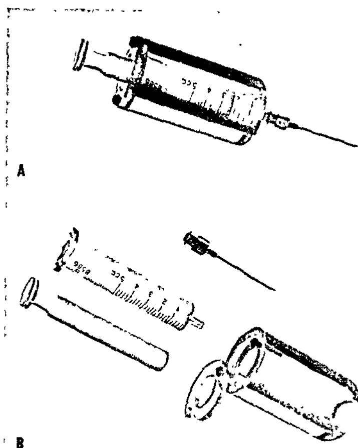


Fig 7—Assembly of syringe with 8 mm thick lucite cylinder for administration of radioactive colloidal chromic phosphate into the pleural cavity, pericardial space or tumor tissue The plastic provides complete radiation protection for the operator from the pure beta emission of P^{32}

change The gold colloid drains to the regional lymphatics, but too slowly to irradiate adequately the regional lymph nodes (Meneely et al) Hahn has therefore prepared radiogold colloid with inactive silver to speed the drainage There is even prompt delivery to the contrilateral lymph nodes after placement in the bronchus Bryant and his colleagues were able to send radiogold colloid to the lymph nodes by injecting the material directly into the bronchial submucosa

The intravascular route has also been explored, using radioactive particles large enough to become fixed in a particular lung segment, after delivery via catheter in a branch of the pulmonary artery (Muller and Rossier). It

has not yet become possible to inject the bronchial artery itself for ideal placement of the radioactive material.

We have already indicated the benefits of supervoltage radiation which Cobalt-60 can provide, as a telecurie substitute for massive x-ray generators. Cobalt-60 is so easily and economically produced that it is finding widespread application in cancer therapy throughout the country as a supervoltage source and as a substitute for radium. It has a half-life of 5.3 years and emits gamma rays of 1.1 and 1.3 Mev. intensity. Cesium-137, with a half-life of 37 years, is another promising high energy nuclear service (0 69 Mev.)

When intractable pleural effusion complicates the life of the patient with advanced carcinoma of the lung, primary or metastatic, it is mandatory that the patient's suffering be relieved by a definitive effort to arrest the formation of fluid This can best be accomplished by the use of radioactive colloidal materials including yttrium, gold and phosphorus in the majority of patients so treated. The nature of the response is not consistently related to any particular type of primary lesion. Indeed, we are convinced that the response is the indirect effect of the impact of ionizing radiation, not on the tumor cell, but on the serous membrane, interfering with the dynamics of fluid transfer.

Radiogold (Au^{198}) has a half-life of 2.7 days, with the emission of mostly beta particles having an average energy of 0 32 Mev and some gamma rays at 0 41 Mev The colloidal gold is nontoxic, insoluble in body fluids and relatively inert biologically. It is introduced intrapleurally in the form of a *colloidal suspension with particles measuring approximately 20 to 200 millimicrons in size* It flocculates on the pleural membrane and produces a superficial and diffuse radiation change with varying degrees of mild fibrous pleural thickening. Occasionally, this thickening may produce extensive adhesions, creating numerous fluid pockets with further limitation of fluid accumulation It is well to point out that the underlying lung tissue is functionally preserved because the maximum range of the beta particles is only a millimeter or two The dosage ranges from 75 to 150 millicuries and this may be followed by more treatment after several weeks, if indicated.

In our clinic, we prefer the use of radioactive phosphorus to radiogold because Au^{198} deteriorates too rapidly, emits a hazardous gamma radiation *and produces only minimal radiation changes on* the surface. Furthermore, in our experience, the gold colloid has failed to flocculate consistently, rapidly or homogenously on the serous membrane. Occasionally, bone marrow depletion has been noted with radiogold therapy.

Radioactive colloidal chromic phosphate has a *half-life of 14 3 days, and* energetic beta particles of 0.7 Mev average energy, with greater penetration of pleura and tumor tissues (up to 8 mm.). The absence of the gamma

ray component provides safety, convenience and economy in preparing, shipping, handling and administering the drug, as well as in the management of the patient after treatment The technic of administration is similar to that employed with radiogold, but is much simpler After removal of the fluid, 10 millicuries of $CrP^{32}O_4$ are injected with a plastic-covered syringe (fig. 7) Our clinical experience of the past five years shows the results to be comparable to those achieved with radiogold Furthermore, isolation of the patient with special ward precautions for radiological safety of hospital personnel is not required. In a series of 50 patients, we have seen no untoward reactions, local or systemic, nor was there any impairment of the blood elements Other investigators have reported a similar experience (Jaffe, Jacobs). Radioactive colloidal yttrium with a pure beta emission of high energy (2 18 Mev) and a short half-life of 2 51 days has not found wide application as yet

Radioactive colloidal materials such as gold and phosphorus have been directly injected into tumor tissue in our clinic and elsewhere A remarkably high dose can thus be introduced into the nonresectable tumor and regional lymph nodes without hazard of damage to surrounding lung tissue However, homogenous distribution of the material is difficult to attain An optimal and consistently effective tumor dose has not been well established Ariel introduced radiophosphorus into many patients with primary and metastatic lung cancer, using intravenous, intra-arterial and intracardiac methods. He concluded that this agent did alleviate troublesome symptoms in a significant number of patients without untoward reactions to the agent

Henschke exploited the use of permanent interstitial seeds of Ir^{192} as a means for dealing with nonresectable lung cancer at operation This agent has a half-life of 74 5 days and emits a high energy gamma ray Accurate localization of the seeds was accomplished with a special gun He reports pronounced tumor regression in nearly every case, worthwhile palliation in many patients and occasional cure The only drawback is the long half-life of Ir^{192}, producing a hazard to the patient's immediate family and associates for several months For this reason, Cr^{51} (with a half-life of 28 days) and Lutetium-177 (half-life 8 days) are being developed

Theoretically, the radioactive isotopes would appear to be the only means of delivering ionizing radiation as a radioactive barb to remote metastatic disease. As yet, however, there appears to be no immediate prospect for specific localization of intensive nuclear radiation in such lesions by metabolic means, as in radioiodine therapy of thyroid carcinoma

In the case of thyroid cancer with pulmonary metastases, it is still necessary to maintain an investigative attitude in spite of the fact that radioiodine treatment has been in progress for nearly 10 years In our labora-

tory, for example, only 3 of our 43 individuals with inoperable thyroid neoplasms were found acceptable for aggressive treatment by virtue of their initial or induced concentration of I^{131}. It should be pointed out, therefore, that the failure of I^{131} to concentrate in pulmonary, mediastinal or hilar metastases from an unknown source does not necessarily exclude the possibility of their being of thyroid origin. Because of the many limitations of radioiodine therapy, no patient with pulmonary or mediastinal metastases *in cancer of the thyroid should be denied roentgen therapy even if isotope* treatment is unfeasible or ineffective. One of our patients, for example, has survived 12 years without evidence of disease after roentgen therapy for far advanced adenocarcinoma of the thyroid involving the mediastinum and one lung field

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CHAPTER 21

Management of Inoperable Primary Tumors of the Chest

By EDGAR MAYER, M D, AND GEORGE C ESCHER, M.D

BRONCHOGENIC CARCINOMA IS NOW the prevailing cancer in the male and its incidence continues on the increase It occurs predominantly between ages 40 and 70 with a peak incidence at about 60 years Its most common form is the epidermoid type found chiefly in the male in contrast to adenocarcinoma which is predominant in the female Other forms are the undifferentiated, the peripheral bronchiolar, the alveolar and the oat cell

Curative resection of lung cancer is possible in fewer than 10 per cent of all the cases that are seen. The total number of the surgically incurable is steadily increasing; therefore, there is need for an active program for their terminal care, employing every feasible palliative weapon

In the management of any patient with lung cancer it is first incumbent on the family physician and the chest internist that they share with the surgeon the responsibility of decision as to surgical intervention Therefore, they should be thoroughly familiar with both the indications and contraindications for surgery

We consider it essential to list here the findings that indicate inoperability in order to emphasize to the practitioner and chest internist the importance of searching for such evidence With this information at hand they will then be able to judge the advisability of surgery

EVIDENCE OF INTRATHORACIC METASTASES INDICATING INOPERABILITY

1 Paralysis of the left recurrent laryngeal nerve, in a patient with recent onset of hoarseness or where bronchoscopy shows vocal cord paralysis

2 X-ray or other evidence of rib or other bony destruction

3 Esophageal constriction or displacement by tumor masses, often accompanied by dysphagia

4 Clinical and radiographic signs of pleural effusion, often bloody, and containing tumor cells (operable only on the rarest occasion)

5 Radiographic or clinical signs of superior vena caval involvement

6 Signs of infiltration of the chest wall, brachial plexus, or of sympathetic chain accompanying apical sulcus tumor

7 Radiographic signs of definite hilar lymphadenopathy, separate from the primary pulmonary cancer.

8 Radiographic or clinical signs of bilateral mediastinal lymph node enlargement ac-

companying a known lung cancer. (Paralysis of the phrenic nerve does not necessarily indicate inoperability if the lesion is otherwise operable, likewise hemidiaphragmatic paralysis does not necessarily indicate malignant invasion of the nerve)

9 Bronchoscopic findings of marked widening of the carina at the tracheal bifurcation, with inflexibility of the lower trachea and main bronchi or definite bronchial fixation, are generally due to mediastinal metastases

10. Bronchoscopic evidence of invasion of the trachea

In evaluating the possible significance of any one of these findings, the clinical picture as a *whole must be taken into consideration before one de*cides that the lesion is definitely inoperable In borderline cases, scalene node biopsy and excision of some upper mediastinal connective or lymphatic tissue through a cervical incision may be recommended. If positive the patient is inoperable.

Distant Metastases

The presence of distant metastases from lung cancer contraindicates surgery in all but the rare instance when significant palliation may be secured surgically The more common distant metastases and the indirect evidence that points to their existence are here enumerated. (When possible, biopsy of such lesions is desirable)

Distant metastases that indicate inoperability are:

1 Palpable firm and large lymph nodes in the cervical region or just behind the clavicle (the softer nodes are less likely to contain metastatic neoplasm, especially those felt in the axillary region).

2 A nodular or grossly enlarged liver

3 Brain metastasis, often evidenced by a recent localized and persistent headache, [illegible] examina- [illegible], electro- [illegible]

4 Bone metastasis anywhere, but more commonly involving a vertebral body, rib, skull or pelvis accompanied by history of localized and recurrent pain of recent onset and often with radiographic changes

5 Suprarenal metastasis with occult or full-blown manifestation of adrenal deficiency.

General Condition of Patient

It is furthermore the particular responsibility of the general practitioner and chest internist to appreciate the operative risk when a question exists regarding the *patient's general condition* The possible benefit derived from *surgery must naturally* be considered in relation to the hazards involved. The operative risk is often dependent to a great extent on the presence of a complicating disease such as serious heart disease, especially in the presence of heart failure (unless a good response to medical therapy is obtained) A history of electrocardiographic evidence of old coronary occlusion is not in itself a contraindication Critical evaluation must be made of complicating emphysema, severe chronic nephritis or essential *systemic*

disorders such as cirrhosis of the liver, diabetes and marked nutritional disturbances. Because of the frequency of pulmonary emphysema in many patients with lung cancer, evaluation of pulmonary reserve is one of the common difficult problems deciding operative risk.

Comprehensive Management

A comprehensive plan of management for the inoperable patient should not only define his present needs, but anticipate all future ones Accordingly, all modalities of treatment must receive due consideration Specific measures for the inoperable patient include *palliative surgery, irradiation and chemotherapeutic measures* Supportive care must be planned to relieve symptoms, improve respiratory function, prolong the period of activity and maintain morale, thus providing maximum comfort at all times The indications and the manner of treatment for reaching this goal of maximum palliation with radiotherapy, with radioisotopes (particularly radioactive colloidal gold, Au^{198}), with chemotherapy (polyfunctional alkylating agents such as nitrogen mustard (HN2) or triethylene melamine (TEM) *intravenously*, leukeran, TEM or myleran *orally*) and *with* palliative surgery are discussed in detail in other chapters

A few words here regarding these measures are in order

Radiotherapy often renders some degree of palliation to most patients with inoperable lung cancer. Obstructed bronchi with infection and atalectasis can thereby be opened up Harassing symptoms such as excessive irritating cough, and expectoration, with dyspnea and fever are not infrequently alleviated

Interstitial radiation therapy through radon seeds implanted at operation into the tumor bed when the cancer is found to be nonresectable is often carried out. In addition empty gold radon-seed capsules can be placed around the periphery of the tumor bed, to be used later as markers for the radiotherapist

The uses of nitrogen mustard *(HN2)* are indicated *in the table* (page 342) It is given intravenously in dosage of 0 4 mg per Kg body weight (25 to 30 mg total dose in the average adult), to be followed by accurate studies of the blood cells and platelets which may become severely depressed This compound may be repeated within six to eight weeks if necessary

In an ambulatory patient *with far advanced disease*, oral *Triethylene Melamine* (TEM) therapy may be given a trial Favorable effect here is less predictable A dosage of no more than 30 to 40 mg in one month should be given, and here also the white blood cells and platelets must be studied carefully and often If TEM is employed intravenously, its dose is 0 12 mg. per Kg body weight. The nausea and vomiting produced by any form of rapidly acting mustard therapy and occurring within one-half

to two hours following injection can be most upsetting. This reaction may be diminished or even controlled by giving Thorazine 0.025 Gm. intramuscularly shortly after injection and repeated in two hours if vomiting is severe. Sodium amytal 0.250 Gm. or 0.120 Gm. sodium phenobarbital intramuscularly may be given on the same schedule for further control

Supportive Measures

In maintaining patient morale, adequate psychotherapy is of prime importance among supportive measures for the patient with inoperable cancer. There is need for encouragement and stimulation by all psychologic means. We have found that frequent careful questioning and thorough physical examinations are essential, so that medication can be given promply for each new complaint. The beneficial as well as undesirable effects of drugs should be discussed openly to acquaint the patient with the underlying reasons for their use One should not hesitate to change the drugs or their dosage frequently, and to enlist the help of the patient in evaluating each new regimen. We must remember that there will always be specific complaints and usually specific causes for them. These are not only a challenge to our therapeutic skill, but present many stimulating *diagnostic problems resulting from the extension of the disease. Without* an open and searching approach we can expect little effect from the medications we employ.

For advancing neoplastic disease with progressive *malnutrition*, high caloric intake should be aimed at, although its administration presents many difficulties. Oral administration of fat emulsions combined with glucose are seldom effectual. The use of vitamin supplements may prove helpful and are apparently more effective if given well diluted intravenously. The development of secondary anemia should be anticipated and treated with transfusions if necessary. We have found iron, liver and B_{12} of little value Interestingly, if the palliative measures have a tumor-restraining effect, improvement in the blood picture can occur without the aid of marrow supporting agents. Iproniazid (Marsilid) in dosage of 50 mg. twice daily has been effective in improving appetite as well as often elevating the morale. During its use watch for impaired liver function

Patients with lung cancer, unlike those with gastrointestinal cancer, rarely present problems in fluid and electrolyte imbalance. The administration of intravenous glucose and protein hydrolysate solutions should be given sparingly. *Adrenal steroids* can be used for the nonspecific effects they induce such as improved appetite and general well-being If cortisone is given we suggest giving it in divided dosages, as follows: 200 mg. total daily dose for two days, 100 mg. for two days, 50 mg. for two days, 25 mg for two or more days. *Nausea may be a distressing symptom, for which*

also a short period of cortisone therapy is helpful Newer forms of corticosteroids are today generally employed in place of cortisone, such as methyl prednisolone (Medrol), triamcinolone (Aristocort, Kenacort), and dexamethasone (Decadron). These have indications and effects similar to cortisone except that some untoward effects have been diminished Sodium and water retention and potassium depletion offer a less serious problem, with these newer varieties Occasionally the administration of testosterone in dosage of 100 mg. intramuscularly three times weekly results in surprising improvement in well-being. When combined with calcium and a high protein intake, androgen therapy may serve to mitigate the catabolic and osteoporotic effects of prolonged steroid therapy

The use of prochlorperazine, a phenothiazine derivative (Compazine) in 5 mg doses four times daily, for a limited period, can control nausea and vomiting and allay anxiety; it has moreover proved helpful in augmenting the sedative effect of barbiturates, due to a side action of somnolence frequently occurring with its use To avert a severe reaction of such nature, dosage should not exceed 15 mg. per dose Derivatives of rauwolfia serpentina can also be given two to three times a day in an effort to control anxiety

A word of caution about overtreatment is in order Continued and vigorous use of parenteral solutions should be avoided as we have found this of little value. Attempting to correct hypoproteinemia by protein infusions is chiefly wasteful and expensive. We usually do not advocate neurosurgery for the control of pain

MEASURES FOR ALLEVIATION OF PULMONARY COMPLAINTS

Too often the patient with inoperable cancer is treated rather haphazardly Constant attention is required in the taking of careful histories and the carrying out of frequent physical examinations if these patients are to receive maximum benefit of treatment

Cough is often a disturbing and difficult symptom to control Treatment of this symptom will depend in part on the type of cough. The patient with an irritating hacking cough that tends to be paroxysmal can be given codeine (¼ to ½ grain every four hours) or dihydrocodeinone bitartrate (Hycodan) in doses of 5 to 10 mg three times a day if required, but if the cough is productive of much purulent sputum, the patient should be instructed in *postural drainage (aside from receiving antibiotics)* Where the cough of itself is productive of much mucoid or mucopurulent sputum, opiates and their derivatives should be used sparingly, since failure to raise bronch[illegible]

telectasis and pneumonitis Both types
of steam vapor and both may receive
onchodilators, administered orally, par-

enterally, by fine mist aerosol or *per rectum*. The newer non-narcotic antitussives such as narcotine (Noscapine) and dextromorphan hydrobromide, (Romilar Expectorant, 15 mg per teaspoonful), or non-narcotic carbetapentane (Toclase 25 mg.) have at times proved helpful. If opiates are indicated we suggest the use of a newer narcotic, L-dromoran, 2 mg. every four hours in preference to morphine, Pantopon, Dilaudid or Demerol. We suggest this because we have found it to have fewer side effects. The use of opiates should not be withheld if needed but should be given with some realization of their harmful effect on the cough reflex. Both cough and dyspnea may be controlled in part by proper positioning of the patient Some appear to benefit from elevating the head of the bed 10 to 18 inches, but others are more comfortable when prone. Patients who have mediastinal involvement usually prefer to sleep with the head of the bed elevated. We have not been impressed with the use of iodides, ammonium chloride and other expectorants in this disease Atropine and antihistamine drugs may so dry the bronchial secretions that the patient is unable to expectorate, and therefore they should be given with caution, if at all. Inhalation of volatile oils (menthol, thymol, oil of eucalyptus) occasionally helps to make coughing easier by increasing bronchial secretions. Spells of strenuous exhausting coughing are often prevented by inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen obtained from a tank to which is attached a reducing valve and flow meter. A "BLB" or "OEM" mask can be used to deliver the gas mixture The meter is set to flow at 5 L./minute and about 20 minute inhalations should be given three times or more daily as needed. If much infection accompanies the cough, the gas mixture can be used as a vehicle for the inhalation of aerosol solutions of antibiotics. The latter should preferably be used after satisfactory cleansing of the bronchi following carbon dioxide-oxygen inhalations.

Hemorrhage is rarely profuse in bronchogenic cancer and then only when the tumor becomes necrotic Frank hemoptyses contraindicate the use of morphine because of cough suppression with retention of blood clots. Codeine or Hycodan are therefore used instead. Rarely are these hemorrhages severe enough to be alarming On occasion, roentgen therapy has effectively stopped bleeding if the bleeding area can be defined. Cauterization of the bleeding point has been rarely attempted by us, and then unsuccessfully.

Bronchospasm is a common condition in patients with inoperable lung cancer requiring medical therapy. The presence of wheezing and night cough should suggest the presence of bronchospasm This can be readily confirmed by ausculation of the lung. Frequently, wheezing is audible through a stethoscope long before the patient experiences asthmatic-like episodes. The vigorous institution of bronchodilator therapy may then make all the difference between a miserable and a relatively comfortable

patient. When evidence of bronchospasm appears, a trial of 25 to 50 mg. ephedrine sulfate with an equal amount of phenobarbital after meals and at bedtime is indicated Occasionally, this results in significant improvement in wheezing as well as in ventilation Not infrequently, however, aminophylline suppositories 0 5 Gm every 8 to 12 hours also are an aid (these should be covered with nupercaine ointment before insertion) If the patient still has episodes of relative discomfort, he should be instructed in the use of an aerosol apparatus, taking 0 5 cc of a 1 per cent Vaponephrin solution as often as needed, to control acute episodes of bronchospasm The intramuscular injection of 1 cc of an 0.2 per cent solution of epinephrine in oil every 12 hours may result in considerable benefit Occasionally, if bronchospasm persists, the administration of 50 mg cortisone four times a day has proved beneficial However usually one of the newer steroids such as prednisone, methylprednisolone, dexamethasone, and triamcinolone, with the fewer and less severe undesirable effects is used in place of cortisone A trial of *isopropyl norepinephrine* (*Isoproterenol*) best administered by aerosol inhalation in doses of 0 1 to 0 5 cc of the 1:200 dilution, may ward off acute episodes of dyspnea For severe symptoms of obstruction with hacking cough, wheezing and difficult raising of sputum, bronchoscopic aspiration and occasionally fulguration have been helpful

Bronchial Obstruction and Infection Patients with inoperable lung cancer almost always have bronchial obstruction of greater or lesser degree *and are particularly susceptible to infection with bronchitis or recurrent* attacks of pneumonitis The clinical aspects of bronchial obstruction are discussed in the chapter on medical aspects As a preventive measure for those with much sputum, the technic of postural drainage should be taught and carried out several times daily, if a trial period proves effective In this way, the tracheobronchial tree will be kept as free as possible of secretions and atelectasis can often be prevented. Signs of pulmonary infection including fever, chills, sweats and change in cough, should receive prompt attention At the first sign of pulmonary infection antibiotic therapy should be instituted. This should consist, at a minimum, of the administration of procaine penicillin, 600,000 U. intramuscularly daily (if the patient is not allergic) together with dihydrostreptomycin 0 5 Gm twice daily, otherwise one of the broad spectrum antibiotics should be used in the common daily dosages At times, retention of secretions behind obstruction may cause a distressing picture of toxemia together with such harassing pulmonary complaints that a palliative surgical resection may be considered for the patient's comfort.

The development of *pleural effusion* often leads to increasing dyspnea Aspiration of such effusions for relief of respiratory distress is indicated and may often be beneficial, but rapid reaccumulation may suggest other

TABLE 1—*Palliative Measures in Inoperable Bronchogenic Carcinoma*

Pathologic Physiology	Clinical Symptoms	Radiotherapy	Surgical Therapy	Medical Therapy
Bronchial proliferation and obstruction	Cough Dyspnea Wheezing Hemoptysis	Palliativ x ray therapy—(3000 r) [illegible] Radon seeds [illegible]	Bronchoscopic drainage fulguration	Nitrogen mustard (HN_2)—0 4 mg/kv I V. Oral alkylating agent Triethylene melamine (TEM) I V. TEM 0 12 mg per K
Pulmonary infection	Fever Chills Cough Expectoration Malaise Toxemia	[illegible]	[illegible]	[illegible] ction [illegible]
Local invasion	Pain	Radiation therapy	[illegible] crosis [illegible]	[illegible]
Pathologic fracture	Pain Disability	Roentgen therapy	[illegible]	[illegible]
Advancing neoplastic disease	Malnutrition Weakness Anxiety Insomnia Anorexia	Radiation therapy 3000 r to multiple areas		High caloric diet ? I V glucose amigen Vitamin supplements Testosterone Corticosteroids Transfusions
Hypoadrenalism due to metastasis	Asthenia			Cortisone Sodium chloride DOCA
Brain invasion	Hemiplegia, etc	Conventional roentgen therapy Marks grid High energy x ray therapy		Nitrogen mustard
Hemoptysis	Anemia Weakness	Roentgen therapy ? Cauterization	Emergency resection, if fulminating	I V nitrogen mustard, medical measures
Pleural *effusion*	*Dyspnea* Disability	*Roentgen therapy* Intrapleural radioactive colloidal gold (Au[198]) Phosphorus 32	*Pleural resection*	*Thoracentesis intrapleural nitrogen mustard*, Au[198] Coll phosphorus 32
Superior vena cava compression syndrome	Severe cyanosis Dyspnea Orthopnea, swelling of head and neck Complete disability	Radiation therapy		I V nitrogen mustard Oxygen Dehydration with Mercuhydrin Diamox Ammonium chloride
Radiation sickness	Loss of appetite, nausea, vomiting, weakness			DOCA Pyridoxine Replace electrolytes and water ACTH Corticosteroids Dramamine Bonamine Chlorpromazine
Radiation pneumonitis				Antibiotics and glucocorticoids
Nitrogen mustard sickness	Nausea Vomiting			Sedation Cortisone ACTH Chlorpromazine

* The measures cited as questionable have not proved useful in our hands, although they have been mentioned as effective by other workers

forms of treatment. Furthermore after repeated tapping, the fluid tends to become loculated and the amount that can be aspirated may be insufficient to be of benefit In these cases, the instillation of nitrogen mustard in dosage of 0.4 mg. per Kg. body weight or radioactive gold (Au^{198}) in dosage 75 to 100 millicuries or radioactive phosphorus (P^{32}) 5 millicuries into

the pleural cavity is carried out. Palliative results with lengthened inter vals between chest-tapping are achieved in about 50 per cent of patient by use of this intracavitary treatment If nitrogen mustard is employed the fluid is first aspirated, followed by a rapid instillation of the dissolve mustard compound. The patient is then rolled for a few minutes from sid to side It is preferable that the patient omit the meal before injection Also one hour before chemotherapy, he is to receive ¾ grain Seconal fol lowed in one-half hour by 25 mg of chlorpromazine The chlorpromazine ha best be repeated 3 times daily (if required) for one or two days depending o the amount of nausea and vomiting Blood cell studies should be made few days after injection. If necessary intrapleural injection may be re peated in one month

Respiratory function can be improved in the *dyspneic* patient with lun cancer by the use of oxygen. This can conveniently be given over a lon period of time through a nasal catheter By this means, the content of oxy gen in the respired air can be increased by as much as 15 per cent Some times, the administration of oxygen by Boothby mask for 20 to 40 minute every two to three hours will add considerable comfort However, its us without supervision is not without danger (In the emphysematous patien whose respiratory center has lost its sensitivity to pH changes of the bloo and who now responds only to oxygen lack, the administration of oxyge removes the main stimulus to breathing (anoxemia) still driving the re spiratory center, and further oxygenation of the blood may result in re spiratory acidosis).

Severe *chest pain* in the patient with cancer of the lung should first b treated with x-ray therapy and/or nitrogen mustard The pain may ofte be due to rib metastasis, and small doses of x-ray therapy over the in volved ribs frequently gives satisfactory relief Other types of chest pai usually respond to the administration of moderate amounts of opiates, wit or without salicylates If the pain is so severe that it is unrelieved b moderate amounts of narcotics, search should be made for evidence of in filtrative involvement of nerve roots such as the brachial plexus If such exists, it is usually less responsive to x-ray therapy Pleuritic pain is fre quently of brief duration, usually disappearing when pleural fluid develops We have rarely found that the use of ethyl chloride spray, local procain injection, intravenous procaine or intravenous alcohol, is indicated in these patients if one makes a careful search for the true cause of the pain We have been disappointed in the use of neurosurgical procedures for the relief of pain. It is often surprising how little opiate a patient requires when the origin of his pain is defined and specifically treated

Lung cancer is prone to *metastasize to bone, brain and liver* The pai from bony metastases anywhere in the body can be controlled by the intel-

ligent use of x-ray therapy We have also been impressed by the remarkable palliation at times of brain metastases from lung cancer when such patients are given x-ray therapy to the entire brain (tumor dose of 3000 roentgens) These as well as liver metastases have been occasionally reported to respond to intravenous nitrogen mustard and/or x-ray With brain metastases best results have been obtained with doses of 25 to 50 roentgens, increasing by the same amount daily five days per week up to the 3000 roentgens midplane dose delivered by a standard deep therapy machine

Metastases *to the mediastinal nodes involving the esophagus* or the recurrent laryngeal nerve with their resultant symptoms of dysphagia, hoarseness, pain etc can at times be favorably influenced by the use of nitrogen mustard and/or radiation therapy.

One of the most distressing syndromes is that of *superior vena cava obstruction*. The clinical picture as well as its treatment with *nitrogen mustard* and/or x-ray has been taken up in greater detail in respective chapters *Nitrogen mustard* (HN2) *has a special place in the therapy of superior* vena caval syndrome due to lung cancer, particularly when followed up by radiation therapy The oat-cell types are especially responsive to HN2 therapy. In addition, this syndrome can often be helped by the vigorous employment of diuretic measures If such patients are given 2 cc. of mercuhydrin *intramuscularly on two successive days, many of their complaints* are ameliorated This can be repeated every week or two provided that the level of the blood chlorides is not decreased too much. If adequate electrolyte control is available, chlorothiazide, hydrochlorothiazide, acetazolamide or ammonium chloride may augment the diuresis or substitute for Mercuhydrin.

When evidence of *adrenal metastases* exists, administration of cortisone may result in dramatic improvement

Attention to the care of the patient with inoperable lung cancer as outlined above yields satisfying rewards Although life is not significantly prolonged, the patient can be made more comfortable Not infrequently, he is able to return to work for long periods and can maintain a hopeful if not entirely cheerful outlook with regard to his health status. Ideally, he should be working part or even full time as long as feasible. This has and can frequently be achieved by meticulous attention to all his complaints A great contrast will then be seen to exist between the patient so handled and one who, through his physician's indifferent, frustrated and careless attitude, has come to accept the hopelessness of his disease

Psychologic Problems

Some final words should be added here regarding the *psychologic* handling of ones *reaction to the existing cancer*. This should take into considera-

tion not only the adjustment or adaptation of the patient but also that of the family. The problem regularly arises as to whether one should be frank in informing the patient of the diagnosis (telling this to a responsible member of the family does not present such a problem). How the patient has handled other life crises is certainly not an infallible guide as to how he will handle the crisis of a threat to his life. Few patients wish to know that they are going to die, yet the steady deterioration of their physical status makes it necessary for them to handle the evidence of their own mortality *How this is done is a highly individual matter*

The group that is perhaps the easiest to manage are those who blandly deny the existence of serious illness at all and frequently show a childlike uncritical faith in the physician A variant of the denying group and far more uncomfortable to handle are those whose denial of the threat is less successful and whose excessive demands for attention and relief of symptoms are in reality frantic attempts to bolster the denial

The emotional response to the cancer and to cancer therapy such as x-ray, must be regarded as a sequence of interrelated reactions With emotions apparent to events taking place at the time and to the patient's perception of these events, what looks like a realistic seeking of medical attention may in fact be panicky flight for help of one who feels himself overwhelmingly threatened. This type of patient may well deceive the doctor into believing that he is dealing with a well balanced person when in fact he is dealing with someone on the verge of disorganization How to handle these varying emotional responses becomes indeed a difficult problem

The physician cannot remain cold and distant but must be seen as a warm and supportive figure whom the patient can trust and with whom he can talk over his preoccupations and ruminations without fear of rejection The physician should not allow his own guilt for being unable to do more than give palliation, tempt him to avoid or abandon the patient Avoidance or abandonment will be interpreted as evidence of hopelessness Moreover, the physician should not neglect the family, for it is often with them that the emotional problems may be most severe and not infrequently become manifest to the patient

Should the doctor tell the patient he has cancer? Certainly this question cannot be answered categorically. Probably most patients can withstand the knowledge that they have cancer without total disintegration but it is never a pleasant experience and serious psychiatric difficulties have been precipitated by it. Moreover, doctors differ greatly in their abilities to handle anxieties as well as to practice the "art of medicine" The "*how*" of telling is often as important as *what* is told, and the relationship existing between physician and patient often eases the way. One need not fully lie to the patient nor wholly tell the truth. In short, the problem of what

to tell the patient and how the patient uses this information can never be predicted in advance by formula It becomes a matter of the most exquisite clinical judgement of the physician as to how, when and how much information is to be imparted to a patient Finally any physician who undertakes the care of a cancer patient must realize that he has assumed an onerous personal burden and that treatment of the physical is only too intimately bound up with that of the psychologic.

Other Inoperable Primary Chest Tumors

Lungs and Pleura

Other tumors of the lungs and pleura are very few in number The commoner ones are *sarcoma and diffuse pleural mesothelioma* Primary *sarcomas* of the lung, although relatively rare, are the diffuse spindle-cell, the peribronchial and the large round-cell varieties The *pleural mesotheliomas* when diffuse are malignant The *localized type of pleural tumor* does occur on occasion and affords a more successful surgical management *Stout has shown that in all probability the localized pleural tumors that* have been reported as fibroma, fibrosarcoma, myxosarcoma, leimyosarcoma and endothelial sarcoma are all variations of the solitary pleural mesothelioma. The diffuse malignant *form* often simulates a pleural *effusion* and is of sanguinous nature. Radiation therapy is indicated, and affords prolonged palliation *in some cases*

Mediastinal Tumors

Primary *neuroblastoma* commonly has its site of origin *in the posterior* mediastinum Its pulmonary metastases almost invariably occur late after bone metastases are present. It often metastasizes to lymph nodes, skin and liver Total extirpation is all too often impossible Unfortunately when most cases are seen, the tumor is no longer localized. Treatment includes *ionizing radiation and chemotherapy* The primary tumor should always be irradiated even when widespread metastases are present. Most all of these are radio-sensitive responding to a tumor dose of 2000 to 3000 r given over two to three weeks X-ray therapy is always considered *to be* worthwhile and even liver metastases may be treated successfully

The nitrogen mustards and anti-folic compounds also exert beneficial effect upon neuroblastoma The mustard effect is brief, for only about six weeks Its use should be immediately followed by x-ray therapy. Then treatment is started *with Amethopterin* (Methotrexate) beginning with a dose of 2.5 mg daily, given orally for several weeks This treatment should be discontinued for two weeks between courses of the drug When recurrence takes place various agents can be tried such as TEM, *corticosteroids* (such as prednisone and prednisolone). ACTH and perhaps even

Coley's toxins. Occasionally one of these agents may produce a remission. Vitamin B-12 therapy in dosage of 1 mg. intramuscularly every other day has been given to children for as long as two years and has shown tumor regression.

Inoperable tumors of the *anterior mediastinum* include teratomas, and some tumors of the esophagus heart and pericardium. In the *middle and posterior mediastinum*, the characteristically inoperable ones are metastatic neoplasms and malignant lymphomas, namely Hodgkin's disease, lymphosarcoma and reticulum-cell sarcoma as well as the leukemias and plasma-cell myelomas. Not infrequently in these diseases, the only lesions at first detectable are those of the pulmonary and mediastinal structures. The treatment of these conditions is taken up in Chapters 12 and 13.

Esophagus

Cancer of the *esophagus* is typically epidermoid, rather malignant and radiosensitive Radiation sterilization of the inoperable case without mediastinitis or severe stenosis from breakdown of the esophageal wall is no longer a rarity Palliation is usually reasonably successful, especially for the fungating and ulcerating tumors, even with medium voltage x-ray therapy. Too high daily and total dosages are best avoided to prevent complications such as perforation and hemorrhage The palliative effect from x-ray treatment is very helpful though temporary Rotation x-ray therapy is preferable. Radioisotopes are also available for palliative treatment. Radioactive iridium is preferable and less costly than small sources of radium, radon, cobalt 60 and gold 198 It is obtainable as separate small sources, loaded into nylon tubing and supplied in a stainless steel enclosed lead container 8" high, 3" diameter weighing 29 pounds, which accommodates 28 nylon tubes Each nylon tube is loaded with 12 seeds spaced 1 cm apart An unloaded tube with a control wire can be placed in the esophagus, then the wire removed and replaced with a small nylon tube loaded with iridium 192 sources Handling is simpler and safer than with radon or radium. Nylon iridium 192 implants may be left in place for one or more weeks (Pack and Ariel)

Heart and Pericardium

Inoperable tumors of the *heart and pericardium* consist of rhabdomyoma, rhabdomyosarcoma, lipoma and myxoma These are essentially rare tumors and no treatment has proved of significant value for palliation

Chest Wall, Ribs and Diaphragm

These structures rarely are the site of primary inoperable tumors These are usually sarcomas and can arise in any of the tissues which constitute

these structures These are usually radiation resistant. No chemotherapeutic agents have shown to be effective (see Chapters 15 and 16).

REFERENCE

1 PACK, GEORGE, AND ARIEL, IRVING M Treatment of Cancer and Allied Diseases N. Y. Hoeber & Co , Publishers, 1958

CHAPTER 22

Management of Metastatic Tumors in the Lungs

By GEORGE C. ESCHER, M.D., AND EDGAR MAYER, M.D.

MANY TUMORS FREQUENTLY METASTASIZE to the lungs, pleura and mediastinum. In the past, treatment modalities were few in number and of extremely limited palliative efficacy.

During the past two decades a steadily and rapidly expanding interest has developed in the management of inoperable tumors. Many disciplines have been enlisted for aid in the development of therapeutic modalities and an expanding list of agents and technics has become available. It should be realized that none of the modalities to be discussed offer more than palliation. There is nothing currently available which can bring about a cure of metastatic malignancy. Most of the agents currently available for palliation also have undesirable effects, some disturbing to the patient, others potentially dangerous.

Not only do different malignancies vary considerably in their rate of growth but an individual tumor in one person will demonstrate periods of apparent quiescence alternating with periods of distinct growth. Since none of the agents available afford more than palliation and as stated above can also have toxic effects it is therefore, important to demonstrate distinct evidence of anatomic progression or the compelling symptomatology before instituting any of the measures to be discussed below. In suspected clinical recurrent metastatic disease one should attempt to establish the diagnosis histologically, rather than simply labelling the patient as recurrent on the basis of previous history of a malignancy and now the development of vaguely suspicious changes. Histological examination of pleural effusion, cytologic examination of sputum, roentgenogram and if the diagnosis is seriously in doubt, actual exploration are helpful in establishing a diagnosis. Symptomatology consisting of weight loss, increased fatiguability, malaise, weakness, dyspnea, cough, chest pain and anorexia is usually of little help since these symptoms are simply indicative of some form of either general illness or pulmonary illness.

ROENTGEN THERAPY

Radiation therapy has been reported on numerous occasions to induce regression of pulmonary parenchymal metastases from various primary

sites. Unfortunately, the postradiation incidence of pneumonitis and fibrosis can be frequent and severe, so that unless radiation therapy has been confined to but a small portion of the lung volume the eventual respiratory embarrassment from radiation damage can be more severe and more rapidly lethal than the original metastatic disease. We, therefore, tend to limit such radiation therapy to an isolated segment of recurrent disease. A tumor dose of 3,000 to 5,000 roentgens is recommended

The problem of mediastinal involvement, however, with its attendant severe respiratory distress and resultant limitation of activity can be relieved in a high percentage of cases with the judicious use of super voltage radiation therapy Ionizing radiation can cause edema, particularly at the onset of treatment If the superior mediastinum is initially exposed to the standard daily dose, the already compromised airway can become occluded. In general, we suggest that radiation therapy be started with a small dose, preferably 50 roentgens increasing by increments of 25 roentgens at first and eventually 50 roentgens. A depth dose of between 3,000 and 5,000 roentgens is usually the goal depending on the radiation sensitivity of the tumor This does not cause much difficulty in the way of radiation pneumonitis and fibrosis. If the tumor is responsive, the patient can have a period of significant improvement in respiratory function.

Occasionally, pleural effusions have been treated with external irradiation through large ports Because of the respiratory impairment resulting from the eventual pulmonary fibrosis, this has in general fallen into discard especially since the demonstrated efficacy of intracavitary use of chemotherapeutic agents and of radioactive isotopes.

Endocrine Therapy

Carcinoma of the Breast

Since pulmonary and pleural metastases are quite common in this type of tumor, considerable experience has developed in the endocrine management of this disease A patient demonstrating such metastasis who is still menstruating or is less than one year postmenopausal should be castrated. Various reports indicate that objective improvement occurs in 40 to 50 per cent of patients castrated Surgical castration is recommended in preference to roentgen castration, because its effect starts on the day of the removal of the ovaries When one removes the ovaries and the adjacent portions of the broad ligament, a relatively complete removal of ovarian tissue and therefore of ovarian function is accomplished.

There are instances where because of physical impairment patients will not tolerate an oophorectomy or the patient, and her family may refuse such procedure. Under these circumstances one could consider and employ roentgen castration to the benefit of the patient. It is recommended that at least 2,000 roentgens depth dose be delivered to the ovaries preferably

over a treatment period of two weeks. It should be remembered that this dose can cause some gastrointestinal disturbance, i.e., diarrhea, cramps, distension, nausea or vomiting. It should also be noted that, in general, six weeks must elapse from the time of completion of said radiation therapy for the maximum depression of endogenous ovarian estrogen production to be accomplished. Therefore, one cannot look for response to such a treatment modality for a minimum of eight weeks after the institution of such treatment. Another reason for recommending surgical versus roentgen castration is that no one has been able to determine accurately what constitutes a totally suppressing dose of radiation therapy to the ovaries since the production of amenorrhea is in no way incontroversial evidence for complete cessation of endogenous estrogen production. Patients have had objective improvement following 600 to 1,200 roentgen depth dose radiation to the ovaries. When the disease eventually escaped from such control in a limited number of patients, bilateral oophorectomy was performed producing a second period of objective improvement.

In patients who are more than 1 year postmenopausal and less than 10 years postmenopausal and those who are no longer responsive to castration, the use of androgens should be considered. The androgens listed in table 1 have been found to be effective.

Common experience indicates that patients who have previously responded to castration stand a much better chance of response to androgen therapy than those who are castration failures. In patients for whom additive hormone therapy is employed, the question of duration of therapy is always raised. It has been found, in general, that 98 per cent of those patients who are going to respond will have responded within three months of the institution of therapy. Therefore, unless the patients show marked evidence of progression or disturbance of function in any one of the various body systems, i.e., salt and water retention, increasing respiratory distress, etc., we prefer to continue such therapy for the minimum period of three months. If a response does occur, patients should be continued on therapy without interruption until such time that there is evidence that the disease is no longer being restrained. Androgen therapy should therefore be stopped if

1. Exacerbation of disease occurs
2. No regression occurs after three months of treatment
3. Regression is no longer maintained

TABLE 1—*Androgen Schedule*

Compound	Dose	Route
Testosterone Propionate	100 mg 3 times per week	Intramuscular
Stanolone	100 mg 3 times per week	Intramuscular
Fluoxymesterone	10 mg 3 times per day	Oral
Methyltestosterone	100 mg 2 times per day	Oral

TABLE 2—*Estrogen Schedule*

Compound	Dose	Route
Diethylstilbestrol	5 mg 3 times per day p c	Oral
Ethinyl Estradiol	1 mg 3 times per day p c	Oral
Sodium Estrone Sulphate	10-15 mg 3 times per day p c	Oral
Estradiol Benzoate	5 mg 3 times per week	Intramuscular

The patient would then be a candidate for another therapeutic regime This should be an antagonist hormone for response categories 1 and 2 and simply cessation of therapy for response category 3. Following cessation of therapy in category 3, regression can again occur so that further treatment with another agent should be withheld until this response to cessation of therapy has lapsed

In the older patient, more specifically, in those patients more than 10 years postmenopausal, estrogen therapy is recommended. Since some of the effects of androgens are more disturbing to women than estrogens are, androgens are usually given parenterally to insure maintainance of therapy whereas estrogens are usually given orally. The problems of anorexia, nausea and vomiting with oral estrogen are usually overcome if one can manage the first two weeks of acute distress either by discussions with the patient or with the added assistance of various antiemetics. In those cases in which the gastrointestinal disturbance cannot be so relieved one can consider injectable estrogen. The following table lists some of the useful members of this group of hormones

The duration of therapy and the cessation thereof is similar to that discussed under androgens One can consider androgens after a period off estrogen therapy Following a trial of androgens or estrogens or a trial of

... con-

... note

that castration failures do not respond to adrenalectomy and rarely respond to hypophysectomy It has been reported that hepatic metastatis is a contraindication to both endocrine ablative procedures and that in addition

...

oophorectomy A maintainance dose of glucocorticoid must be taken regularly and supplements given at times of stress. The hypophysectomy patients also require thyroid extract and posterior pituitary extract. During the past few years the number of bilateral adrenalectomies has diminished while hypophysectomy has been increasing.

... response to either es-

...orticoids listed

in table 3. These can be very salutary in their effect on many of the clinical

TABLE 3—*Glucocorticoid Schedule*

Compound	Dose	Route
Cortisone	200 mg daily	Oral
Hydrocortisone	160 mg daily	Oral
Prednisone	40 mg daily	Oral
Prednisolone	40 mg daily	Oral
6-Methylprednisolone	32 mg daily	Oral
Triamcinolone	32 mg daily	Oral
Dexamethasone	6 0 mg daily	Oral

signs and symptoms that accompany involvement of the pulmonary system but their side effects can also be quite troublesome Some of the newer substituted compounds cause less difficulty with sodium retention and potassium loss; nevertheless, these can still cause difficulty even with the latest of the substituted agents The various manifestations of Cushingoid syndrome will still occur; the moon facies, the striae buffalo hump, mental disturbance, diabetes mellitus, peptic ulcer, uncomplicated or hemorrhaging or perforating can occur It should also be noted that these various complications may necessitate cessation of said glucocorticoid therapy This cannot be done abruptly in those cases who have had any extended period of treatment In order to avoid an Addisonian crisis a gradual tapering off of glucocorticoid and the temporary administration of ACTH is often necessary

The objective improvement rate with androgens is in the vicinity of 20 per cent and the regression rate with estrogens is in the vicinity of 25 to 30 per cent Reports on the response to glucocorticoids have been so variable that a reliable percentage figure is not currently available

ALKYLATING AGENTS

If pleural effusions do not respond adequately to such systemic hormone therapy one should consider the intracavitary use of the polyfunctional alkylating agents. The one acting most rapidly and with which there has been the greatest amount of experience is methyl bis (B-chloroethyl) amine (nitrogen mustard, HN2) The recommended dose is 0 4 mg per Kg body weight, prepared in a saline solution usually in a concentration of between 0 5 to 1 mg per cc. of normal saline Following thoracentesis to dryness the dissolved nitrogen mustard is injected into the pleural cavity

If bilateral pleural effusion needs such treatment it is suggested that only nitrogen mustard 0 2 mg per Kg body weight be employed in each pleural space. We usually recommend placing the patient in a horizontal position moving patient from side so side so that there can be adequate distribution of the medication This need not be done for more than a few minutes because the agent is fairly well fixed by body proteins quite rapidly

TABLE 4—*Isotopes for Effusions*

Isotope	Intrapleural Dose	Half life	Emission
Gold—AU^{198}	75–100 mc	2 7 days	Beta and gamma
Phosphorus—$CrP^{32}O_4$	5 mc	14 3 days	Beta
Yttrium—Y^{90}	10–30 mc	2 5 days	Beta

In general, there is little to no systemic reaction to intrapleural mustard Prochlorperazine, 10 mg or chlorpromazine hydrochloride 30 mg can be given prophylactically.

The problem with superior vena caval syndrome as mentioned in Chapter 22 is quite distressing. It has been found that the polyfunctional alkylating agents can be very helpful therapeutically; in general, since the problem is usually quite acute, we have recourse to nitrogen mustard rather than some of the slower acting members of the polyfunctional group The dose recommended varies from 4 to 6 mg per Kg body weight given intravenously. Antiemetics and barbiturates given prior to the intravenous administration of nitrogen mustard can help control the sometimes distressing vomiting.

ISOTOPES

If the polyfunctional alkylating agents do not afford adequate control of the formation of effusion we usually recommend the use of one of the radioactive isotopes. Three different radioactive isotopes have been used

These have produced a significant degree of control over pleural effusion. Reports vary but in general the average range of response is between 40 and 50 per cent

SPECIFIC METASTASES

Carcinoma of the Prostate

Pleural and pulmonary metastases are less frequent in patients with carcinoma of the prostate In general, it is agreed that regardless of age the most efficient therapeutic measure is castration. Surgical castration is so simple in the male and the risks and complications so minimal that it is rare that anything but orchiectomy is done Estrogens have been found to be of assistance. The following table lists the estrogens and their recommended doses.

The question of the efficacy of estrogens in those who are no longer responsive to castration has been raised and is currently under study. Adrenalectomy and hypophysectomy have been tried in inoperable prostate carcinoma with indifferent results. Therefore relatively few have been done within recent years Radioactive isotopes and polyfunctional alkylating agents are of some value in effusions similar to those found in women with breast cancer

Carcinoma of the Thyroid

Thyroid carcinoma frequently metastasizes to the lung Significant ectopic uptake of I^{131} can establish the diagnosis of metastatic thyroid carcinoma The rare exception is functional thyroid tissue in the dermoid tumor Such ectopic uptake in metastases, however, can only occur in the absence of normal functional thyroid tissue

I^{131} may be used to destroy metastatic foci Since the thyroid gland has a greater affinity for I^{131}, it must first either be surgically removed or destroyed by external radiation, i e., 4,800 roentgen tumor dose or by treatment with I^{131}. Following the destruction of the gland the patient is given TSH (thyroid stimulating hormone) to increase the endocrine function of the metastases and thereby increase I^{131} uptake After a tracer dose of I^{131} demonstrates enhanced uptake, a therapeutic dose thereof varying from 35 to 80 millicuries, depending on the total lung tumor mass, is given Higher dose I^{131} treatment in the presence of fairly bulky pulmonary metastases can produce radiation pneumonitis and fibrosis with their subsequent very serious sequelae. Reports of objective regression around 50 per cent have been published The histologic type usually responsive to such treatment is the alveolar follicular carcinoma I^{131} is a beta and gamma emitter with a half-life of eight days

Toxicity can be radiation illness 24 hours after I^{131} administration Hematologic changes can approach pancytopenia Thyroiditis, gonadal damage and hepatic dysfunction have been observed

Carcinoma of the Ovary

Metastases to the lung and pleura from serous and pseudomucinous cystadenocarcinomas of the ovary are usually late phenomena Chorioepithelioma metastasizes early and diffusely to the lung Endocrine therapy has been disappointing in ovarian carcinoma Under conditions previously described radiation therapy can be of some palliative value The alkylating agents have produced 10 to 20 per cent objective improvement in several series of metastatic adenocarcinomas of the ovary

1 TEM (triethylene melamine) orally 5 to 10 mg 90 minutes before breakfast for a total dose per course of from 20 to 40 mg with maintenance thereafter dependent of the hematologic status, i e , platelets above 100,000, WBC above 3,000

2 CB 1348 (chlorambucil) orally 6 to 20 mg daily for a total course between 300 to 400 mg

TABLE 5—*Dosage Schedule*

Compound	Dose	Route
Diethylstilbestrol	5 mg daily	Oral
Ethinyl Estradiol	0 5 mg daily	Oral

The folic acid antagonist, methotrexate, in a dose schedule of 2.5 mg daily for four days at weekly intervals for about four to five courses when the hematologic picture permitted, has produced dramatic and prolonged objective regression in women with metastatic chorio-epithelioma Some have demonstrated no reappearance of metastatic foci two to two and one-half years after the initial course of treatment. Parenthetically, choriocarcinoma of the testis is unresponsive to methotrexate

Carcinoma of the Gastrointestinal Tract

Carcinomas of the stomach and of the large intestine can metastasize to the lungs, pleura and mediastinum Radiation therapy has given short-lived palliation within its limited scope of usefulness in a tumor that not infrequently is radioresistant. The alkylating agents and most of the better known antimetabolites have been disappointing as chemotherapy in advanced G I. carcinomas However, preliminary studies with fluorinated pyrimidines demonstrated enough significant and extended regression to warrant expanded trials with this group of agents. It is possible that other tumors of the gastrointestinal system, i.e., liver, pancreas, or gall bladder may also be responsive

Carcinoma of the Kidney

Radiation therapy may occasionally afford palliation for metastases to the respiratory system from renal carcinoma. Wilm's tumor, which has a high rate of pulmonary metastases, has demonstrated a significant rate of regression to treatment with actinomycin D intravenously. The initial course of therapy is 0 5 mg daily for five successive days Signs of toxicity are anorexia, nausea and vomiting with depression of the WBC and platelets More recently actinomycin KS 4 has demonstrated a similar effect.

Other tumors of the kidney have demonstrated no significant responsivity to currently available chemotherapeutic agents.

Malignant Melanoma

All of the various chemotherapeutic agents available within the past decade have been tried in malignant melanoma. There have been occasional reports of a single response to an agent. Confirmation by other investigators has usually been lacking.

CHAPTER 23

Systemic and Peripheral Manifestations of Neoplasms

By DAVID M SPAIN, M D.

THE PRESENCE OF A NEOPLASM in the body may be related to or associated with diverse systemic or peripheral manifestations that are usually not directly related to the local destructive effects of the tumor or to the effects of metastases on the cells of other organs In many instances, the nature of the relationship between the tumor and the systemic or peripheral manifestations remains obscure In others, it appears more clearly defined In some cases the presence of such peripheral manifestations may antedate for varying periods the clinical detection or local symptoms of the primary tumor itself. In still others these may appear as terminal events Detection and removal of the primary tumor sometimes reverses some of these systemic syndromes Tumors must be considered more than just space-occupying and mechanically infiltrating masses Their complex enzyme systems, products of their metabolism and immuno-allergic potentialities, undoubtedly play a dynamic role in relation to the total body s physiognomy There is also a general group of host adaptations that are related to the presence of a tumor These include the vague condition related to wasting and malnutrition commonly known as cachexia, plasma protein changes alterations in liver and adrenal function and anemia [8]

SYSTEMIC INFECTION

Infection as a complication of malignant neoplasm occurs basically in two broad patterns One is the local infection that develops secondary to mechanical effects of the tumor In this situation, the tumor produces obstruction of various ducts and channels, compression with ulceration of lining surfaces or obliteration of blood supply to vital areas These are conditions which predispose towards the development of infection The other broad category is the development of systemic infection that is based on some general alterations in the host's resistance This latter situation is seen most characteristically with neoplasms of lymphatic tissue, bone marrow or reticulo-endothelium system At present it is not uncommon to find a variety of systemic fungus infections that have complicated lymphosarcoma, Hodgkin's disease and reticulum cell sarcoma Analysis of these

same malignant conditions many years ago indicated that systemic infections were perhaps just as prevalent but were caused by different organisms. Currently, the use of various antibiotics and chemotherapeutic agents has altered both the internal bacterial flora, as well as the external contaminants, so that systemic infections are now caused by a different group of offenders. These include histoplasma, cryptococcus and various atypical organisms. Tuberculous infection as a complication is seen less frequently than in the past, but the use of steroids in some of these neoplasms has activated and spread latent or dormant tuberculous foci. The basic distinction between the effects on the host's resistance to infection in carcinoma, as compared to the neoplasms that arise from the reticulo-endothelial and lymphatic systems, is that the neoplasms of the latter group involve not only those cells believed to be responsible for the production of antibodies, but the scavenger and phagocytic cells as well. In some of these conditions, abnormal globulins are manufactured, and there is also alteration in usual levels of serum gamma globulin. Likewise, some chemotherapy specifically directed against these tumors is often destructive of marrow, lymphoid tissue and reticulo-endothelial cells. It is believed therefore that these are the basic mechanisms in this latter group of neoplasms that tend to favor the development of systemic infections These mechanisms are not interfered with in the presence of carcinoma in which most of the infections are secondary to the local mechanical effects of the tumor. It is not uncommon for some of these cases at post-mortem examination to contain only scant residual morphologic evidence of the original neoplastic process, but yet reveal extensive evidence of a widespread infection

THROMBOTIC SYNDROMES

Occasionally an unsuspected carcinoma is accompanied by multiple venous thromboses. Infrequently, this thrombotic syndrome may present itself with nonbacterial vegetations on the cardiac valves that result in arterial and arteriolar emboli with visceral infarction. Sometimes, the onset is in the form of a migrating thrombophlebitis. This thrombosis may begin while the patient is fairly active and may even be the first sign of disease. This occurrence cannot be considered merely as an agonal or terminal event. In one group of 29 cases of migrating thrombophlebitis associated with carcinoma, the pancreas was the primary site of tumor in 16 cases. The stomach and lungs were each the primary site four times Peripheral thromboses have also been seen associated with tumors of the colon and ovarian teratomas These thrombotic phenomena are more frequent than has been generally recognized The superficial veins of the upper and lower extremities are the sites most frequently involved but no area is entirely exempt Pulmonary emboli are frequent.[3, 4, 7, 10]

The pathogenesis of these thrombi still remains unclear. It appears to

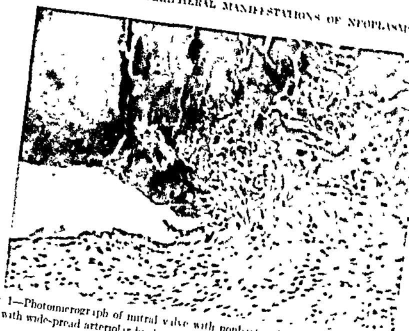


Fig 1—Photomicrograph of mitral valve with nonbacterial thrombo-endocarditis associated with widespread arteriolar hyaline-like thrombi in a case of bronchogenic carcinoma

be unrelated to the frequent thrombosis of the vessels in the immediate vicinity of a tumor. The local thrombi that occur in the vicinity of the tumor do not account for the distant thrombi or emboli. Changes in the factors concerned with blood coagulability have been considered but as yet no proof is available. The suggestion that at least in carcinoma of the pancreas the digestive enzymes escape into the circulation with resultant damage to the vascular endothelium is an attractive hypothesis. Recently, collagenase has been found in pancreatic juice and has been implicated as a possible factor that might also damage vascular endothelium. Arteriolar and capillary occlusions have also been seen in patients with carcinoma but much less frequently than venous thrombi. These hyaline-like thrombi are similar to those seen in thrombotic thrombocytopenic purpura. The material composing these thrombi appears to be a fibrinoid substance according to the most recent histochemical studies. Its presence has been attributed to an immuno-allergic mechanism in which the vascular walls may represent the shock site. This may be based on autosensitization to the proteins of the organism.

Hypertrophic Pulmonary Osteoarthropathy

Generalized hypertrophic pulmonary osteoarthropathy is actually a syndrome consisting of clubbing of the fingers and toes, periosteal bone formation in the shafts of the larger long bones of the extremities and a form of arthritis [illegible] associated with disease

of the thoracic viscera This form of clubbing is to be distinguished from congenital clubbing which is unassociated with periosteal thickening and which is not related to pulmonary disease. Bronchogenic carcinoma is the neoplasm most frequently associated with this change. As with some of the other peripheral manifestations of tumors, it may be the first sign that directs attention to the presence of a tumor. It has also been found with metastatic tumors to the lung, benign lesions of the mediastinum and pleura and more recently with a neurilemmoma of the diaphragm. It is seen more frequently in males than in females even when allowance is made for the greater frequency of bronchogenic carcinoma in males This symptom complex will vary with the exacerbations and remissions of the underlying primary disease so that surgical removal of a tumor may produce a reversal of the manifestations If there is local recurrence or metastases, the hypertrophic pulmonary osteoarthropathy may recur. Pathogenesis of this condition is unknown. Theories range from the elaboration of toxins by altered pulmonary tissue or degenerating tumor to changes in the dynamics of the peripheral circulation[1]

Sensory and Motor Neuropathy

A combination of sensory neuropathy with polyneuritis has been observed most characteristically with intrathoracic forms of cancer, especially with carcinoma of the lungs and esophagus It is estimated that about 2 per cent of all lung cancers may be complicated by spinal cerebellar ataxia, sensory neuropathy, polyneuritis and neuromuscular disturbances. These changes are not caused by carcinomatous invasion of the nervous system. The posterior column degeneration that occurs at times may be more extensive than that seen in tabes dorsalis.

In one group of 19 cases the neurologic symptoms antedated the diagnosis of the tumor. In one instance there was an interval of 28 months between the onset and recognition of the neurologic manifestations and the [illegible]

this neuropathy is also unknown Viruses, toxins, nerve [illegible] and vitamin E disturbances have all been implicated[13]

The Symptom Complex of Dermatomyositis and Other Connective Tissue Disturbances

The acute form of dermatomyositis is seen in association with neoplasms. Reports of at least 70 such cases have been recorded In one collected group of 45 patients with dermatomyositis, 8 developed some form of malignant neoplasm between the ages of 27 and 39. In all instances the neoplastic process has preceded the cutaneous and muscular changes In some of these

cases the final detection of the tumor has awaited post-mortem examination In a few, the dermatomyositis has regressed following successful removal of the neoplasm The dermatomyositis does not become aggravated with progression of the tumor. Although extrathoracic primary neoplasms arising in the ovary, breast, stomach and reticulo-endothelial system are more frequently associated with this acute form of dermatomyositis, it has also been seen with such intrathoracic neoplasms as carcinoma of the lung and esophagus[2, 5]

The skin lesions in this form of dermatomyositis are erythematous and the distribution as well as the microscopic morphology mimics systemic lupus erythematosis Usually, edema is not present This form of dermatomyositis should be separated from the chronic progressive dermatomyositis that is unassociated with neoplasms This syndrome may be related to nerve degeneration that may occur with malignant disease, perhaps predicated upon competition by the tumor cells for the same essential nutritional factor.

The association of scleroderma with cancer of the lungs is of a different nature. It is likely that scleroderma actually precedes the bronchogenic carcinoma. The atypical alveolar epithelium seen with the fibrotic process in the lungs of patients with scleroderma may be the precursor for the development of cancer.

Other connective tissue disturbances seen particularly with bronchogenic carcinoma are arthralgia and arthritis of the rheumatoid type In one group of cases, arthralgia was the initial clinical disturbance in 4 per cent Eighteen of 24 patients with fibrous mesothelioma of the pleura had symptoms and signs referable to the joints The relationship of this phenomena to the production of hyaluronic acid by mesothelial tumors may have some significance. Often, these manifestations are also associated with pulmonary osteoarthropathy

The relationship of lupus erythematosis to carcinoma appears to be no more than coincidental There was a 2 per cent occurrence of carcinoma in a group of 374 patients with systemic lupus erythematosis that were followed for at least a five year period[11]

The Metastatic Carcinoid Syndrome

Only recently it was thought that the carcinoid form of bronchial adenoma was not related histogenetically to the intestinal carcinoid Intestinal carcinoids arise from the argentifine cells that are present in the intestinal mucosa. It was not thought that bronchial adenomas of this type were capable of producing a 5-hydroxytryptamine (serotonin) However, a number of cases of malignant bronchial adenoma of the carcinoid type with the systemic and peripheral manifestations of hyperserotonemia have now

been reported In some of these cases, biochemical evidence of increased serotonin production was found in the urine in the form of its breakdown product—5-hydroxyindolacetic acid This may be determined by a rather simple test. It has been described with increasing frequency in recent years in associated with metastatic carcinoid of the small intestine. The basic findings of this syndrome consist of chronic diarrhea, flushes, cyanosis, respiratory distress and right-sided cardiac disease. Most of these manifestations are the result of excessive secretion of serotonin from the tumor tissue. The serotonin acts on the smooth muscle of the blood vessels, trachea and intestine. Some of the findings may be due to depletion of the body reserves of tryptophane which is utilized in the synthesis of these large amounts of serotonin. The changes in the skin, especially of the face, include teleangectasia and dilatation of the small vessels. This appears to be due in part to a local plethora, but there is no over-all increase in the number of red blood cells In most cases there are episodic attacks of flushing associated with extreme cyanosis At times these are combined with such vasomotor manifestations as sweating and hot sensations In some, there are recurrent episodes of cyanosis, respiratory symptoms akin to bronchial asthma. The patient may be dyspneic and have a respiratory stridor. The blood pressure remains relatively normal during the attack. Mental disturbances may occur but are difficult to evaluate in seriously ill patients. Clinical records contain such descriptions of the patients with this syndrome as uncooperative, unreliable, contradictory and very nervous. In the advanced form of this syndrome there may be cardiac disturbances with predominantly right-sided heart failure based on the production of fibrostenotic lesions on the pulmonary and tricuspid valves [11]

Hematologic Dyscrasias

There are obviously numerous hematologic dyscrasias associated with lymphoma—whether it be generalized or limited to the thoracic cage. The hemolytic anemias, hypersplenic manifestations require no comment at this point Neither does the leukemoid reaction that may be secondary to metastases in the bone marrow from bronchogenic carcinoma.

Recently secondary polycythemia has been noted in certain renal diseases and especially in carcinoma of the kidney This is said to be related to an increase in an erythropoetic factor thought to be elaborated in the kidney This finding is of particular significance as regards the differential diagnosis of chest neoplasms when it is remembered that carcinoma of the kidney metastasizes to the lungs in 75 per cent of the cases Thus, the appearance of an undiagnosed neoplastic-like shadow in the chest in the presence of secondary polycythemia should focus attention on the kidney as the most likely primary site. Clamping of the renal vein has produced

a similar type of secondary polycythemia as has certain benign tumors, polycystic kidneys and hydronephrosis.[8, 9]

Anemias secondary to carcinoma are generally nutritional in origin in the majority of instances even when the bone marrow is extensively involved with metastases

Sarcoid-like Granulomas in Lymph Nodes

The lymph nodes that drain an organ involved with carcinoma may contain granuloma indistinguishable from those seen in Boeck's sarcoid There is nothing specific about any of these granulomata since a wide variety of agents may provoke this type of reaction These granulomata have been seen in axillary lymph nodes in association with carcinoma of the breast, in perigastric lymph nodes in cases of stomach carcinoma, and more recently in scalene fat-pad lymph nodes in cases of bronchogenic carcinoma The finding of such granulomata in tissue removed at a scalene biopsy in the presence of a hilar or mediastinal shadow may at times mislead one into believing Boeck's sarcoid is present, when in actuality the lesion is a neoplasm How frequently this occurs remains to be determined.[15]

Phospholipids that are released from necrotic tumor tissue may be absorbed by a regional lymph node and may be responsible for provoking this reaction. It is well known that lymph nodes that drain diseased gallbladders contain granulomata as a reaction to lipid substances [16]

Amyloidosis

Amyloid, a homogenous acidophilic staining substance that is usually found between cells of glandular organs or mesenchymal tissues, may occur during the course of mediastinal Hodgkin's disease, less frequently with lymphosarcoma and rarely with bronchogenic carcinoma Amyloid is actually a group of substances which are believed to be proteins precipitated in an antigen-antibody reaction These extracellular proteins have in common a free aldehyde group which reacts with such stains as iodine-acid, Congo red, silver salts and leukofuscin Hepatosplenomegaly may occur and confuse the picture of the underlying neoplasm If renal involvement is marked, there will be a nephrotic syndrome The formation and deposition of amyloid may be a response to a hyperimmune reaction associated [illegible] the proteins or reticuloendothelial proliferation of some neoplasms.

Recently, in the experimental animal cortisone and nitrogen [illegible] have enhanced the formation of amyloid It also appears that [illegible] mustard has stimulated more rapid amyloidosis in human cases of [illegible] sarcoma. In mediastinal Hodgkin's disease or lymphosarcoma the [illegible] ment of the spleen at times may represent amyloidosis and not [illegible] spread of the neoplasm.[13, 14]



Fig 2—Photomicrograph of extensive amyloidosis in bone marrow of a case of rapidly developing amyloidosis following treatment of lymphosarcoma with nitrogen mustard

Hypercalcemia

Alterations in calcium metabolism have been noted with many malignant tumors, both in the presence and absence of bone destruction from osseous metastases The effectiveness of sex steroid hormones, as well as exacerbations of skeletal metastases in patients receiving such treatment for breast cancer, may be detected by hypercalcemia Determination of the degree of hypercalcemia is also of value in the evaluation of other new anticancer chemotherapeutic agents. The application is made easier by recently developed simplified, precise and quantitative technics for the assay of calcium *in various biologic fluids*

Summary

Systemic manifestations of neoplasms are diverse and include infection, *dermatomyositis, arthritis, hypertrophic osteoarthropathy,* amyloidosis, blood dyscrasias, thrombotic syndromes and more specific disturbances secondary to secretions from certain functioning tumors. Undoubtedly, in the future more of these systemic relationships will be uncovered and understanding of the currently observed ones will increase.

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